CLINICAL REVIEW

Application Type	NDA
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Division/Office	DNH (Division of Nonmalignant Hematology)
Reviewer Name(s)	Sabrina McClintock
Review Completion Date	See date stamp
Established/Proper Name	Ticagrelor
Trade Name	Brilinta
Applicant	AstraZeneca Pharmaceuticals LP
Dosage Form(s)	Tablets
Applicant Proposed Dosing Regimen(s)	N/A
Applicant Proposed Indication(s)/Population(s)	N/A
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	None

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Glossary

AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

AstraZeneca has conducted a set of studies to evaluate ticagrelor (Brilinta®), an oral, reversible, antiplatelet agent, as a potential treatment for reduction in the rate of vaso-occlusive crises (VOCs) in pediatric patients with sickle cell disease (SCD). Ticagrelor demonstrated an unfavorable benefit-risk profile in the Phase III study, HESTIA3; therefore, the study was terminated early. AstraZeneca concludes that the results do not support a pediatric indication for ticagrelor in this treatment setting.

Ticagrelor has an established, positive benefit-risk profile for the prevention of atherothrombotic events in adult patients with cardiovascular disease. Ticagrelor 90 mg twice daily, after a loading dose of 180 mg, was approved by the FDA on 20 July 2011 for reduction in the rate of thrombotic cardiovascular events in adult patients with acute coronary syndromes. An extended indication, for ticagrelor 60 mg twice daily, to include adult patients with a history of myocardial infarction was approved on 03 September 2015. On 28 May 2020, the FDA approved a further extended indication for ticagrelor 60 mg twice daily to reduce the risk of a first myocardial infarction or stroke in patients with coronary artery disease at high risk for such events. Most recently, ticagrelor 90 mg twice daily (for up to 30 days) was approved on November 5, 2020 to reduce the risk of stroke in patients with acute ischemic stroke or high risk transient ischemic attack.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Ticagrelor demonstrated an unfavorable benefit-risk profile in the Phase III study, HESTIA3; therefore, the study was terminated early. AstraZeneca concludes that the HESTIA3 results do not support an indication for ticagrelor in this treatment setting; thus, they are not applying for a pediatric indication for the treatment of sickle cell disease and the FDA agrees.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment
Ticagrelor demonstrated an unfavorable benefit-risk profile in the Phase III study, HESTIA3; therefore, the study was terminated early. AstraZeneca concludes that the HESTIA3 results do not support an indication for ticagrelor in this treatment setting; thus, they are not applying for a pediatric indication and the FDA agrees.

Table 1 Benefit Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Sickle cell disease is a genetic, autosomal, recessive blood disorder resulting in an altered hemoglobin β chain (HbS). • When the altered hemoglobin is deoxygenated, it aggregates into large polymers, distorting the shape of the red blood cells to sickle-shaped. The disease is associated with hemolytic anemia, significant chronic end organ damage, and early death. In high income countries, about 95% of children with the disease survive into adulthood, resulting in a growing population of affected adults with significant co-morbidities and complex medical issues.	Sickle cell disease is a life-threatening disease associated with comorbidities affecting all organ systems and premature death, especially if left untreated.
Current Treatment Options	• Hydroxyurea: increases HbF • L-Glutamine: mechanism unknown • Voxelotor: inhibits sickling • Crizanlizumab: Binds to P-selectin on the surface of activated endothelial cells and platelets • Stem cell transplant in high-risk patients who have a donor source	There continues to be a high unmet need for treatment options in SCD. Only a small percentage of patients with SCD are eligible for a possible cure with stem cell transplantation due to lack of stem cell donors and high cost of this treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• No clinical benefit was demonstrated in patients with sickle cell disease.	No evidence of clinical benefit for ticagrelor over placebo was observed in pediatric patients with SCD; therefore, the risks are unacceptable.
Risk and Risk Management	• The proportion of patients reporting SAEs was higher on ticagrelor; this was driven by events of Sickle cell anemia with crisis. In addition, 3 patients in the ticagrelor group and 1 patient in the placebo group died during the study.	No indication for SCD will be granted. No risk management is needed.

1.4. Patient Experience Data

Table 2 Patient Experience Data

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Sec 6.2
		☒	Observer reported outcome (ObsRO)	Sec 6.1.2, 6.2
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☒	Patient-focused drug development or other stakeholder meeting summary reports	Sec 2.1, Analysis of Condition
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

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Sickle cell disease (SCD) is a genetic, autosomal, recessive blood disorder resulting in an altered hemoglobin β chain (HbS). In all sickle cell genotypes, at least 50% of the patient's hemoglobin is HbS. The HbS gene is common in the Caribbean, Central and South America, the Middle East, Africa, and India. In African Americans, the prevalence of HbSS is approximately 1 in 600, and the prevalence of all disease genotypes approaches 1 in 300. SCD affects approximately 100,000 Americans, occurs in about 1 out of every 365 Black or African American births and 1 out of every 16,300 Hispanic-American births (Centers for Disease Control and Prevention, 2022).

There are several forms of SCD: HbSS (discussed above; also called sickle cell anemia); HbSC; HbS beta thalassemia; HbSD; HbSE; and HbSO. Patients with HbSS receive two sickle cell genes ("S") (1 from each parent) and usually have the most severe form of the disease. Patients with HbSC inherit a sickle cell gene ("S") from one parent and an abnormal hemoglobin gene ("C") from the other parent. HbSC is usually a milder form of the disease. Patients with HbS beta thalassemia inherit one sickle cell gene ("S") from one parent and one gene for beta thalassemia (another type of anemia) from the other parent. There are two types of beta thalassemia: "0" and "+". Patients with HbS beta 0-thalassemia usually have a severe form of SCD and those with HbS beta +-thalassemia usually have a milder form of SCD. The rarer types of SCD include HbSD, HbSE, and HbS0 and the severity of these SCD types is variable. Sickle cell trait (HbAS) occurs in people who inherit one sickle cell gene ("S") from one parent and one normal gene ("A") from the other. People with trait usually do not have any of the signs of SCD and live a normal life, but they can pass on the trait to their children. (Centers for Disease Control and Prevention, 2022)

SCD is diagnosed (typically at birth through newborn screening) using a hemoglobin electrophoresis test.

When the altered hemoglobin is deoxygenated, it aggregates into large polymers, distorting the shape of the red blood cells to sickle-shaped. The disease is associated with hemolytic anemia, vasoocclusive crises (VOC), significant chronic end organ damage, and early death. In high income countries, about 95% of children with the disease survive into adulthood, resulting in a growing population of affected adults with significant co-morbidities and complex medical issues. A VOC is a severe, acute painful episode that occurs when sickle-shaped red blood cells obstruct the microcirculation and restrict blood flow to an organ or tissue, resulting in ischemia, necrosis, and organ damage. The clinical presentation varies depending on the localization of the obstruction, which can occur essentially anywhere in the body (head to toe) and when severe, can be life-threatening. Vasoocclusion in the cerebral vessels can present as a stroke. A common cause of death in this population is acute chest syndrome (ACS) where the pulmonary vasculature is affected. Splenic vasoocclusion can lead to splenic sequestration, and splenic auto-infarction renders these patients immunocompromised for life. Bony infarcts and/ or avascular necrosis can lead to severe and painful osteoarthritis and collapse of the bone

segment leading to significant disability. Priapism is not uncommon in males. The most common initial clinical manifestation in children is dactylitis, vasoocclusive crisis in the fingers, that causes pain and swelling. VOC pain crises can also occur anywhere in the body and regularly require narcotic analgesics for relief. Clearly, this is a disease, that even with adequate treatment, can greatly negatively affect quality of life. Vasoocclusion is initiated and sustained by complex interactions among sickle cells, endothelial cells, and constituents of plasma (Pecker L, 2021).

Activated platelets participate in the process by promoting the adhesion of sickle cells to the endothelium, and through the formation of platelet-leukocyte aggregates, which augment the inflammatory state and contribute to vasoocclusion. In patients with SCD, platelets are activated during the non-crisis 'steady state' and are further activated during painful episodes. Markers of platelet inhibition have been shown to correlate with the frequency of pain crises (Ataga KI, 2012).

On February 7, 2014, FDA conducted a public meeting on Patient-Focused Drug Development for sickle cell disease where we asked patients affected by SCD to tell us how SCD impacted their daily life and what they thought about available therapies for sickle cell disease. Approximately 140 patients or patient representatives attended the meeting (in person and via a live webcast). The meeting results were summarized in a report titled "The Voice of the Patient: Sickle Cell Report". The patient input summarized in this report described the serious nature of SCD, the complexity of treatment, and the broader challenges that patients face in getting the care and support that they need. Patients described their experience with SCD as causing excruciating and incapacitating episodic pain crises and acute chest syndrome. They also noted the pervasive effects of chronic pain, fatigue, cognitive effects, and temperature sensitivity. Older participants described the debilitating impacts stemming from progressive damage to blood vessels, organs, tissues, and bones. Women shared their experiences with (or fears about) pregnancy. Participants of all ages expressed fear about dying early from their disease. Participants stated that SCD impacts all aspects of their lives, limiting their ability to perform in school, pursue careers, have a family, and maintain relationships. The disease takes an emotional toll as patients face challenges with the healthcare system, stigma within society, financial hardships, and worry about their future. (FDA, 2014)

2.2. Analysis of Current Treatment Options

Until recently, the only pharmacological treatment approved for reduction of VOCs was hydroxyurea. Hydroxyurea reduces the rate of painful crises, ACS, and the need for blood transfusions in adults and children with SCD (Charache S, 1995), (Wang WC, 2011), but patients need to be closely monitored since hydroxyurea causes myelosuppression and has other side effects. Since 2017, three new drugs for the treatment of sickle cell disease have been

approved by the USFDA (Endari, Oxbryta, and Adakveo). In July 2017, the US FDA approved L-glutamine (Endari) for the reduction of acute complications of SCD; however, with the limited experience with L-glutamine and current approval only in the US, the role of this compound in the treatment paradigm remains to be established. Although the frequency of SCD complications is reduced with hydroxyurea and with L-glutamine, most patients continue to suffer from these complications despite treatment. Crizanlizumab (Adakveo), a P-selectin inhibitor, was approved by the FDA in November 2019 to reduce the frequency of VOCs in adults and pediatric patients aged ≥ 16 years with SCD. The orally administered hemoglobin S-polymerization inhibitor, voxelotor (Oxbryta), was also approved by the FDA in November 2019 for adults and pediatric patients ≥ 12 years of age with any form of SCD.

The only curative treatment for sickle cell disease is stem cell transplantation and while its use is increasing, candidacy depends on the patient's disease type, their age, their complications (multiple pain crises, poor response to hydroxyurea, history of acute chest syndrome, and/or stroke), and whether an appropriate donor is available. Transplant morbidity and mortality increases significantly starting in early adolescence.

Other commonly used supportive treatments include red blood cell (RBC) transfusions (for treatment of the associated anemia), hydration (oral and intravenous), and non-opiate and opiate pain medications (to relieve SCD acute and chronic pain). Blood transfusions are used as both acute and chronic therapy. The primary goal in both types of therapy is to reduce the HbS concentration below 30%. Indications for emergent transfusion include acute stroke or other central nervous system injury, acute chest syndrome, sickle cell hepatic crises, or multisystem organ failure. Chronic exchange transfusions are indicated in children with abnormal results on transcranial Doppler screening and in children and adults with a history of stroke or evidence on MRI of cerebrovascular disease. Repeated transfusions are associated with iron overload, alloimmunization, and blood related infections.

Despite the availability of these new medications, there continues to be a high unmet need for treatment options in SCD. The above-described approved medications provide modest improvement in the symptoms of the disease. Further, there are many adult patients who opt out of treatment due to concern of the late of effects of hydroxyurea, especially with respect to fertility and carcinogenesis (Su Z, 2019). Gaps in evidence persist; evidence is weak for the 30% of patients with HbSC, HbSβ^+, and other compound heterozygous disease types. Hydroxyurea is not FDA approved for these disease types because there have been no randomized controlled trials of hydroxyurea for these patients. In addition, although the new agents are approved for these disease types, small numbers of participants were included in the phase 3 trials (Pecker L, 2021).

Table 3 Available Treatments for Sickle Cell Disease

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information
Hydroxyurea DROXIA	Adults with moderate - severe SCD	2003	Oral Titrate to maximally tolerated dose or 35 mg/kg of body weight per day	Median yearly rate of painful crises: DROXIA 2.5 vs Placebo 4.6 (P = 0.001) Median yearly rate of painful crises requiring hospitalization: DROXIA 1.0 vs Placebo 2.5 (P = .0027) Median time to 1st painful crises (mo): DROXIA 2.76 vs Placebo 1.35 (P = 0.014) Median time to 2nd crises (mo): DROXIA 6.58 vs Placebo 4.13 (P = 0.0024) Incidence of ACS (# episodes): DROXIA 56 vs Placebo 101 (P = .003) # of pts transfused DROXIA 55 vs Placebo 70 (P=0.002) # of units blood transfused: DROXIA 423 vs Placebo 670 (p = 0.003)
Hydroxyurea SIKLOS	Pediatric patients ≥2 yrs with SCD with recurrent moderate-severe painful crises	2017	Oral Titrate to maximally tolerated dose or 35 mg/kg of body weight per day	Patients w/ at least one VO episode: 12 mo prior to HU = 69.2% and 42.5% after HU. Median # of VO episodes 12 mo before HU: 2.0; After 12 mo of HU: 0
L-Glutamine ENDARI	Reduce acute complications of SCD in adult and pediatric patients ≥5 yrs	2017	Oral 10-30 g/day (based on body weight), twice daily. Beverage. Each dose to be mixed with 8oz of fluid or 4-6 oz of food before ingestion	Median number of crises through week 48 (crisis requiring ED visit, or ACS, priapism, or splenic sequestration): ENDARI 3 vs 4 Placebo Median number of hospitalizations for SC pain: ENDARI 2 vs 3 Placebo Median cumulative days in hospital: ENDARI 6.5 vs 11 Placebo Median days to first SC crisis (95% CI): ENDARI 84 vs 54 Placebo Patients with occurrences of ACS: ENDARI 8.6% vs 23.1% Placebo
Voxelotor OXBRYTA	Adult and pediatric pts with SCD ≥12	2019	Oral 1500 mg/day	An increase of Hb of >1 g/dL from baseline to week 24 for 1500 mg of Oxbryta was observed in 51.1% (46/90) patients compared to 6.5% (6/92) in placebo group (p<0.001).

	yrs			
Crizanlizumab ADAKVEO	Reduce frequency of VOCs in adults and pediatric patients ≥16 yrs	2019	Intravenous 5 mg/kg per infusion w/ first 3 infusions at 2 week intervals + subsequent infusions monthly	Annual rate of VOCs leading to a healthcare visit requiring treatment with oral or parenteral opioids, or parenteral NSAIDs (Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism also considered VOC): Adakveo : 1.63; Placebo: 2.98 P=0.010

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ticagrelor is a $P2Y_{12}$ platelet inhibitor approved for marketing as Brilinta in the U.S. on July 20, 2011 and indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome or a history of myocardial infarction. Ticagrelor also reduces the risk of stent thrombosis in patient who have a history of acute coronary syndrome. Since initial NDA approval, additional approved indications are to reduce the risk of first myocardial infarction or stroke in patients with coronary artery disease at high risk for such events, and to reduce the risk of stroke in patients with acute ischemic stroke (National Institutes of Health Stroke Scale score ≤5) or high risk transient ischemic attack.

3.2. Summary of Presubmission/Submission Regulatory Activity

AstraZeneca first discussed the proposal to evaluate ticagrelor in pediatric patients with SCD with the FDA's Division of Hematology Products (now Division of Nonmalignant Hematology) at a pre-IND meeting on 15 January 2014. Subsequently, the first pediatric study protocol (HESTIA1) in the SCD program was submitted to IND 120,366 on 18 March 2014 and received a "Study May Proceed" letter on 7 April 2014.

AstraZeneca submitted a Proposed Pediatric Study Request to IND 120,366, on 21 February 2019 (Sequence/Serial No. 0254) to seek a Written Request from the FDA to conduct two Phase III safety and efficacy studies (HESTIA3 and HESTIA5/D5136C00013) and one Phase I PK study (HESTIA4) in pediatric patients with SCD. On 21 June 2019, AstraZeneca received such a Written Request from the FDA, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007. Along with the Written Request detailing the requirements for those 3 studies, AstraZeneca received an agreed iPSP which provided FDA's agreement on the necessary waiver for the age range

from birth to 6 months.

The HESTIA3 study was stopped early at the recommendation of the Data Monitoring Committee due to an imbalance in deaths and futility. AstraZeneca notified FDA of these events immediately and subsequently discussed the high-level results and early termination of HESTIA3 with the FDA at a Type C meeting with FDA on 23 February 2021. At this meeting, the FDA agreed that continuation of studies to evaluate ticagrelor in pediatric patients with SCD would be inappropriate. At the time of the recommendation to terminate HESTIA3 early, the second Phase III study HESTIA5 was ready to start in the US and the United Kingdom, with a number of US sites prepared to enroll patients. Once the decision was made not to expose any further pediatric patients to ticagrelor, the initiation of HESTIA5 was terminated, and subsequently, the FDA agreed with the removal of HESTIA5 from the Written Request.

Table 4 provides a chronological summary of the regulatory interactions between AstraZeneca and the FDA on the Ticagrelor Pediatric Program in patients with SCD.

Table 4 Summary of Interactions with the FDA on the Ticagrelor Pediatric Program in Patients with Sickle Cell Disease

FDA response to PPSR (revised PPSR submitted 7 June 2018)	02 July 2018	FDA issued an Inadequate Study letter. AstraZeneca subsequently submitted a further revised PPSR (dated 12 February 2019).
FDA response to iPSP submitted on 29 May 2018	23 August 2018	AstraZeneca received a Written Response from FDA, including comments consistent with the Inadequate Study letter, and subsequently submitted a revised iPSP on 21 February 2019.
Receipt of FDA Written Request and agreed iPSP	21 June 2019	The Written Request detailed the requirement for 3 studies (HESTIA3, HESTIA4, and HESTIA5).
Teleconference to discuss early termination of HESTIA3	28 July 2020	A team of AstraZeneca senior managers firewalled from the Brilinta Paediatric Development Team discussed the reasons for the early termination of HESTIA3 with FDA.
FDA response to Written Request Amendment and receipt of FDA Inadequate Study Letter	20 August 2020	FDA agreed with AstraZeneca's proposed amendment (submitted 30 April 2020) to the statistical analysis methods for HESTIA3 and the planned HESTIA5 study but advised that they were unable to issue an amended Written Request due to the early termination of HESTIA3. The FDA requested submission of a new, amended PPSR.

Interaction	Date	Key discussion points and agreements
Type C meeting	23 February 2021	Presentation and discussion of the high-level results of HESTIA3. FDA agreed that continuation of clinical studies to evaluate ticagrelor in paediatric patients with sickle cell disease would be inappropriate. FDA also agreed that continued development and marketing of an age-appropriate paediatric formulation was not warranted.
FDA issued Written Request Amendment 1	12 August 2021	FDA agreed with the removal of the planned HESTIA5 study from the Written Request.

IND, Investigational New Drug application; iPSP, Initial Pediatric Study Plan; PPSR, Proposed Pediatric Study Request.

Source: Applicant Submission

3.3. Foreign Regulatory Actions and Marketing History

Interactions with EMA

In the EU, a PIP (EMEA-000480-PIP01-08-M14) was agreed for the evaluation of ticagrelor in pediatric patients with SCD. On 18 June 2020, AstraZeneca notified EMA in writing that the independent DMC for HESTIA3 had recommended that AstraZeneca terminate the study). In December 2020, AstraZeneca submitted a proposed modification to the PIP, to remove the obligation to develop age-appropriate pediatric formulations, based on the outcome of HESTIA3. The PDCO agreed with AstraZeneca's conclusion that there is no role for ticagrelor for the treatment of SCD in a pediatric population and approved the removal of the pediatric formulations from the PIP in March 2021. Full compliance with the agreed PIP was granted on 02 July 2021. Following approval of an update to the EU Summary of Product Characteristics based on the pediatric studies, AstraZeneca received the Statement of Compliance and EU Commission Decision on a fully completed PIP on 29 September 2021.

As of October 28, 2020, Health Canada's review of the available information concluded that there may be a link between the use of Brilinta and the risk of central sleep apnea. Health Canada stated they will work with the manufacturer to update the Canadian product safety information for Brilinta to add a warning about central sleep apnea safety issue.

In a communication to the FDA from Health Canada, (b) (4)

(b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit of the clinical trial data submitted to the application was not requested because the Applicant has not requested an indication and no indication will be granted.

4.2. Product Quality

There was no CMC module submitted for this supplement. Therefore, no CMC review was conducted.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There was no nonclinical module submitted to the supplement. No nonclinical review was conducted.

4.5 Biostatistics

The biostatistical reviewer was Huan Wang, PhD and his Team Leader is Yeh-Fong Chen. The executive summary from is review is below.
In this submission, the Applicant submitted the sNDA for ticagrelor to fulfill the WR requirement for pediatric exclusivity. As specified in the WR Amendment 1, this sNDA contains the study report of Study 1 (D5136C00010, i.e., HESTIA4), a Phase I study investigating the pharmacokinetic properties of ticagrelor in pediatric patients from 0 to less than 24 months with SCD, and also Study 2 (D5136C00009, i.e., HESTIA3), a Phase III study evaluating the effect

of ticagrelor versus placebo in reducing the rate of vasoocclusive crises (VOCs) for pediatric patients with SCD.

The pivotal Phase III study HESTIA3 was an international, double-blind, randomized, parallel-group, placebo-controlled study. On 15 June 2020, the Applicant received a recommendation from the Data Monitoring Committee (DMC) to terminate the HESTIA3 study, on the grounds that "the risks to patients of continuing the study outweigh any possibility that ticagrelor may show a beneficial effect if the study were completed". The Applicant agreed with this recommendation and as a result of the premature termination, the end of study visit was defined by a common study end date (18 June 2020) corresponding to the date of communication to all investigators to immediately discontinue administration of investigational product for all patients who were still on study treatment. The study was fully recruited at the time of the DMC recommendation, with 193 patients randomized at 53 sites across 16 countries in Africa and Asia, Europe, and North and South America.

In the HESTIA3 study, the primary efficacy variable (number of VOCs) had a higher incidence rate in the ticagrelor group (2.74 per year) than in the placebo group (2.60 per year) with an incidence rate ratio of 1.06 (95% CI: 0.75, 1.50; P-value = 0.7597), which demonstrated that ticagrelor was not superior to placebo in reducing the rate of VOCs.

4.6. Clinical Pharmacology

The clinical pharmacology reviewers was Snehal Samant, PharmD and Jihye Ahn, PharmD for Pharmacometrics. Their Team Leaders were Sudharshan Hariharan and Liang Li, respectively. The following is a portion of the executive summary from her draft review.

This sNDA contains the results for Study D5136C00010 (HESTIA4) and Study D5136C00009 (HESTIA3), as specified in the Written Request Amendment 1 (August 12, 2021). HESTIA4 is a Phase I study which investigated the pharmacokinetic properties of ticagrelor in pediatric patients of age 0 to less than 24 months with sickle cell disease. HESTIA3 is a Phase III study which evaluated the effect of ticagrelor versus placebo in reducing the rate of vasoocclusive crises (VOCs) in pediatric patients with sickle cell disease. The unfavorable benefit-risk profile (including imbalance in deaths and failure to demonstrate an effect on the primary endpoint) of ticagrelor in pediatric patients (aged ≥2 years to <18 years) with sickle cell disease in HESTIA3 resulted in the termination of this study. This study was modified in the amended Written Request to account for the early termination. The Applicant has proposed an update to the current approved BRILINTA prescribing information Section 8.6 to reflect the negative outcome of HESTIA3 and to avoid potential off-label use.

The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology (OCP/ DCEP) has reviewed the clinical pharmacology information contained in NDA 022433/ Supplement 34 and finds it acceptable.

4.7. Devices and Companion Diagnostic Issues

No companion device or diagnostic is included in the application.

4.8. Consumer Study Reviews

No consumer study reviews were included in the application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 5 Listing of Relevant Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration + F/U	No. of pts enrolled	Study Population
HESTIA1 (D5136C 00007)	2-part study in pediatric patients ages 2 to <18 years with SCD. Part A: randomized, multicenter, open-label PK and PD dose-ranging phase II study of Ticagrelor. Part B: double-blind, randomized (2:1 ratio), parallel-group, placebo-controlled 4-week extension phase in pediatric patients with SCD (Part B was designed to provide preliminary data on efficacy and tolerability, but was made optional in a protocol amendment) 10 Study locations	Part A: the treatment period consists of 2 single doses (separated by at least 7 days) followed by 7 days open label ticagrelor treatment twice daily. Part B: patients randomized to 4 weeks twice-daily treatment. There is no washout period between Part A and Part B.	1. P2Y12 Reaction Units (PRU)- 2. Maximum Plasma Concentration (C_{max}) 3. Area Under the Plasma Concentration Time Curve (AUC)	Total expected study duration for an individual patient participating in both Part A and B is approximately 3 mo (including 30 days follow-up after last dose) and approximately 2 mo for an individual patient participating in only Part A (including 30 days follow-up after last dose).	46	pediatric patients ages 2 to <18 years with SCD.
HESTIA3 (D5136C 00009)	International, multi-center double-blind, randomized, parallel group, placebo-controlled Phase III study to evaluate the effect of ticagrelor versus placebo in	The double-blinded study drug dose was weight dependent and taken orally: • ≥ 12 to ≤ 24 kg: 15 mg (1 tab) of ticagrelor or 1 tab of	Number of VOCs	Subjects received double-blind ticagrelor or placebo BID for at least 12 -24 mo. The expected average follow-up was	193	Pediatric patients ≥2 yrs to <18 yrs with HbSS or HbS/β^0 SCD who had experienced at least 2 VOC events in previous 12 mo

	reducing the rate of VOC events in pediatric patients with SCD 53 sites across 16 countries	placebo BID • > 24 to ≤ 48 kg: 30 mg (2 tab) of ticagrelor or 2 tab of placebo BID • > 48 kg: 45 mg (3 tab) of ticagrelor or 3 tab of placebo BID		18 m. Because of premature study termination, the end of study visit was defined by a common study end date. All pts had their IP stopped by 23 June 2020, approximately 4 mo earlier than estimated		
HESTIA4 (D5136C 00010)	Phase I pediatric study in patients aged 0 months to <24 months, multi-center, open-label, single-dose study. 8 study centers in 6 countries	20 with SCD were planned to receive a single dose of ticagrelor. Four PK samples were to be taken up to 6 hours post-dose (1, 2, 4 and 6 hours post-dose) from each patient. Lab safety samples were collected before administration of the single dose and repeated at a follow-up visit that took place within Day 4 to Day 8.	Observed plasma concentrations as well as PK parameters obtained using a population PK analysis approach, eg, CL/F (oral clearance), C_{max} and AUC	Eligible patients received a single open-label oral dose of ticagrelor on Day 1. There was a screening period from Day-7 to to Day 1 and a follow up period from Day 4 to Day 8.	23	Pediatric patients: birth to < 24 months with SCD.

5.2. Review Strategy

The application is being reviewed by the clinical, statistical and clinical pharmacology disciplines. The applicant stated that HESTIA3 did not achieve the primary endpoint. They are not seeking a pediatric indication. Therefore, the results of this trial were not verified down to the source data. This review document is authored by the primary clinical reviewer, Sabrina McClintock and Team Leader, Virginia Kwitkowski. No other disciplines authored this document with the exception of executive summaries included in Section 4.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. HESTIA4

6.1.1. Study Design

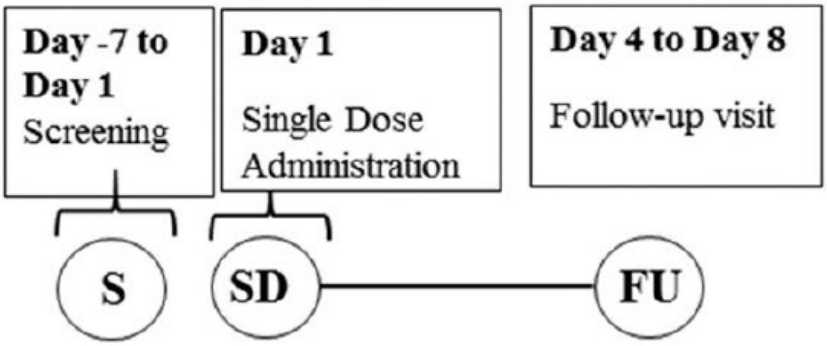
Overview and Objective

D5136C00010: The HESTIA4 study is entitled "A Multi-center, Phase I, Open-label, Single-dose Study to Investigate Pharmacokinetics (PK) of Ticagrelor in Infants and Toddlers, Aged 0 to less than 24 Months, with Sickle Cell Disease."

The primary objective of this study was to determine the PK properties of ticagrelor after a single oral dose. The secondary objectives were to determine the PK properties of the active metabolite (AR-C124910XX) after a single oral dose and to assess the acceptability and the palatability of a single oral dose. The safety objective was to assess safety and tolerability of a single oral dose of ticagrelor.

Trial Design

Figure 1 Flow Chart of Study Design (HESTIA4)



S: screening; SD: single dose administration; FU: follow-up visit.
Screening procedures, including laboratory testing for haematology, clinical chemistry and coagulation could have been performed on the day of single dose administration (Day 1), if the weight of the participating patient allowed for drawing the necessary total volume of blood, and if results were available before dose administration.

Source: Applicant submission

This Phase I pediatric study (in patients aged 0 months to <24 months) with ticagrelor was planned as a multi-center, open-label, single-dose study. Twenty patients with SCD (homozygous sickle cell anemia [HbSS] or sickle beta-zero-thalassemia [HbS/β^0]) were planned to receive a single dose of ticagrelor. Four PK samples were to be taken up to 6 hours post dose (1, 2, 4 and 6 hours post dose) from each patient. The total number of samples and volume of blood samples were to be compliant with the European Ethical Considerations in a Pediatric Population 2008 (Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population 2008). In case the total volume of blood taken would have exceeded the ethics limit for any patient, the 1-hour post dose PK sample could have been omitted in order to fulfil the ethical considerations. Additional patients could have been recruited to ensure at least 20 evaluable patients completed the study.

During the study, patients were to be evaluated for adverse events (AEs)/serious adverse events (SAEs) and with laboratory safety samples and measurement of vital signs. Serious adverse events were to be collected from the time of signature of informed consent throughout the treatment period and including the follow-up period. Adverse events were to be collected from administration of ticagrelor (Day 1).

Laboratory safety samples were to be collected before administration of the single dose and repeated at a follow-up visit that was to take place within Day 4 to Day 8. A schematic

representation of the study design is shown in Figure 1.

There were no unusual design features in this study. The design was fit for the purpose.

This was a multi-center study conducted at 8 study centers in 6 countries (Belgium, Italy, Kenya, Lebanon, Spain, and the United Kingdom). Given this is a PK study, there is no concern regarding applicability of the results to the U.S population.

The diagnostic criteria for enrollment was that patients have SCD (homozygous sickle cell anemia [HbSS] or sickle beta-zero-thalassemia [HbS/β^0]). The criteria would select a population similar to the target population in the U.S. The criteria definitions do not pose any problems.

The key inclusion criteria were pediatric patients aged <24 months, diagnosed with HbSS or HbS/β^0, who were ≥5 kg at the time of screening, otherwise, overall healthy without major SCD complications, and if taking an anti-sickling agent, on a stable dose for 3 months before screening/ enrollment.

No unnecessary exclusions were identified. Exclusion criteria was as follows:

- History of transient ischemic attack or cerebrovascular event (ischemic or hemorrhagic), severe head trauma, intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy.
- Significantly underdeveloped with regards to height, weight, or head circumference for age, as judged by the investigator
- Severe developmental delay (eg, cerebral palsy or mental retardation)
- Received chronic treatment (>3 days/week) with nonsteroidal anti-inflammatory drugs (NSAIDs).
- Received chronic treatment with anticoagulants or antiplatelet drugs that could not be discontinued.
- Moderate or severe hepatic impairment
- Renal failure requiring dialysis.
- Active pathological bleeding or increased risk of bleeding complications according to the Investigator.
- Hemoglobin <6 g/dL from test performed at screening (Visit 1).
- Platelets <100 × 109/L from test performed at screening (Visit 1).
- Patient considered to be at risk of bradycardic events (eg, known sick sinus syndrome or second- or third-degree atrioventricular block).
- Concomitant oral or intravenous therapy with moderate or strong CYP3A4 inhibitors, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers
- Active untreated malaria.
- Surgical procedure planned to occur during the study including 5 days after ticagrelor administration.

- Known hypersensitivity or contraindication to ticagrelor.

This was the first study with ticagrelor in children <2 years old with SCD. The doses chosen for this study were a single oral 0.1 mg/kg dose of ticagrelor in the age group <6 months and a single oral 0.2 mg/kg dose of ticagrelor in the age group ≥6 months.

For selection of doses in this study, a pediatric physiologically based PK (PBPK) model was developed based on physiochemical, in vitro and final PK data from children aged 2 years to <18 years in HESTIA1 study (D5136C00007). The model was used to predict ticagrelor exposure in children in the age groups of 0 to <6, 6 to <12, and 12 to <24 months, respectively. The proposed doses were selected to enable detection of both ticagrelor and the active metabolite in plasma after a single dose without causing a pronounced degree of platelet inhibition. The predicted level of reduction in platelet reactivity unit (PRU) at the predicted maximum concentration for the selected doses was close to but did not exceed 50%. The dose level could have been adjusted during the study for subsequent patients based on the emerging results from this study to ensure evaluable plasma exposure data while minimizing the risk for pronounced platelet inhibition. Any such dose adjustments required a CSP amendment and regulatory approval. Further, any proposed dose adjustments were to be selected to ensure no more than 50% reduction in PRU.

Study treatment is demonstrated in Table 6.

Table 6 Study Treatment (HESTIA4)

	Treatment
Study treatment name:	Ticagrelor
Dosage formulation:	Granules for oral suspension 10 mg
Route of administration:	Oral
Dosing instructions:	A single oral 0.1 mg/kg dose of ticagrelor for the age group <6 months and a single oral 0.2 mg/kg dose of ticagrelor for the age group ≥6 months. Before administration, ticagrelor granules were constituted with 10 mL of purified water to form a homogenous suspension of 1 mg/mL ticagrelor.
Packaging and labelling:	Study treatment was provided in glass bottles. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory guidelines.
Provider:	Almac Pharma Services

Source: Applicant submission

This was an open-label, non-randomized study; therefore, no randomization of patients occurred, and no blinding procedures were applicable.

The dose level may be adjusted during the study for subsequent patients based on emerging results from the study to ensure evaluable plasma exposure data while minimizing the risk for pronounced platelet inhibition. Any such dose adjustments will require a Clinical Study Protocol (CSP) amendment and regulatory approval. Further, any proposed dose adjustments will be selected to ensure no more than 50% reduction in PRU.

This was a multi-center study conducted at 8 study centers in 6 countries (Belgium, Italy, Kenya, Lebanon, Spain, and the United Kingdom). The Coordinating Investigator was Dr. Baba Inusa MRCP, FRCPCH, DCP (Haem), FMCPaed; Evelina London Children's Hospital. Administrative structure further consisted of study personnel at the study centers and AstraZeneca study personnel. No Safety Review Committee was used during the study. However, AstraZeneca representatives in consultation with the AstraZeneca Patient Safety Department closely monitored the safety of all the patients in this clinical study on an ongoing basis.

Table 7 summarizes the study plan including the procedures and assessments conducted at each timepoint.

Table 7 Schedule of Assessments (HESTIA4)

Assessment	Screening[a]	Treatment	Follow-up
Visit: **Day:**	**1** **Day -7 to Day 1**	**2** **Day 1**	**3** **Day 4 to Day 8**
Signed informed consent	X		
Inclusion/exclusion criteria	X	X	
Relevant medical and surgical history, SCD characteristics and history	X		
Demographics	X		
Vital signs (BP, pulse)	X	X	X
Physical examination	X	X	X
Body temperature	X	X	X
Weight	X	X	X
Height	X		
Head circumference	X		
12-lead ECG[b]	X		
Administration of ticagrelor at study centre		X	
Compliance/study treatment accountability		X	
Acceptability/palatability		X	
Concomitant medication	X	X	X
Adverse event review (AEs and SAEs)	X	X	X
Blood samples for haematology and clinical chemistry[b]	X		X
Blood samples for coagulation (INR and PTT)[a]	X		
Blood sampling for pharmacokinetics[c]		X	

[a] Screening procedures, including laboratory testing for haematology, clinical chemistry and coagulation could have been performed on the day of single dose administration if results were available before dose administration and provided that the weight of the participating patient allowed for drawing the necessary total volume of blood (in practice 10 kg or more).

[b] If any results from ECGs and blood samples were taken before the signing of informed consent as part of the standard medical care, these could have been used for screening purposes at the discretion of the Investigator and if they were taken within 7 days of study treatment administration.

[c] Four PK samples were to be taken up to 6 hours postdose (1, 2, 4 and 6 hours postdose) from each patient. The total number of samples and volume of blood samples were compliant with the European Ethical Considerations in a Paediatric Population 2008 (Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population 2008). In case the total volume of blood taken would have exceeded the ethics limit for any patient, the 1-hour postdose PK sample could have been omitted in order to fulfil the ethical considerations.

AE: adverse event; BP: blood pressure; ECG: electrocardiogram; INR: international normalised ratio; PK: pharmacokinetic; PTT: partial thromboplastin time; SAE: serious adverse event; SCD: sickle cell disease.

Source: Applicant submission

Grapefruit juice in the amount of >5 dL/day (approximately 2 cups) was not allowed.

The following concomitant procedures/medications were not allowed during the study:

- Treatment with an anti-sickling agent such as hydroxyurea, if the weight-adjusted dose had not been stable for 3 months before screening/enrolment.
- Surgical procedure during the study including 5 days after ticagrelor administration
- Concomitant treatment (>3 days/week) with NSAIDs.
- Concomitant treatment with anticoagulants or antiplatelet drugs.
- Concomitant oral or intravenous therapy with moderate or strong CYP3A4 inhibitors, CYP3A4 substrates with narrow therapeutic indices or strong CYP3A4 inducers.

A detailed list of prohibited concomitant medications is as follows:

1. Platelet aggregation inhibitors: NOT ALLOWED
   - Other ADP receptor blockers – clopidogrel, prasugrel, ticlopidine, cangrelor
   - Dipyridamole
   - Cilostazol
   - Aspirin

2. Anticoagulants: NOT ALLOWED
   - Coumarins – warfarin
   - Heparins (except for flushing venous catheters prior to sampling)
   - Factor Xa inhibitors – fondaparinux, apixaban, rivaroxaban, edoxaban
   - Thrombin inhibitors – bivalirudin, dabigatran, argatroban, desirudin, lepirudin

3. Non-steroidal anti-inflammatory agents: NOT ALLOWED if chronically used, requiring treatment >3 days/week.
   - Propionic acid derivates – ibuprofen, dexibuprofen, naproxen, ketoprofen
   - Acetic acid derivates– indomethacin, ketorolac, tolmetin, sulindac, diclofenac

- Enolic acid derivates – piroxicam, meloxicam, tenoxicam
- Selective COX-2 inhibitors – celecoxib, parecoxib, etoricoxib
- Others – clonixin

4. CYP3A4 inhibitors: NOT ALLOWED as they substantially increase ticagrelor exposure.
    - Strong inhibitors – atanazavir, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
        - Please note that the above compounds are not allowed for mothers who breastfeed any patients during the study.
    - Moderate inhibitors – amprenavir, aprepitant, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, macrolide antibiotics (ie, erythromycin; (but azithromycin IS ALLOWED), fluconazole, fosamprenavir, imatinib, verapamil

5. CYP3A4 substrates or inducers: NOT ALLOWED as they reduce ticagrelor exposure and may result in reduced efficacy.
    - Rifampin/rifampicin
    - Rifabutin
    - Rifapentine
    - Phenytoin
    - Carbamazepine
    - Phenobarbital
    - Avasimibe
    - St. John's wort
    - Simvastatin/ Lovastatin (metabolized by CYP3A4- increases their concentration – avoid doses greater than 40 mg)

6. P-glycoprotein interactions
    - Digoxin –If the patient is receiving digoxin, levels should be monitored closely following initiation of IMP and with any change in IMP
    - Cyclosporine – NOT ALLOWED as it increases ticagrelor exposure

The administration of IMP was to be recorded in the appropriate sections of the eCRF. The IMP provided for this study will be used only as directed in this protocol. The study center personnel accounted for all IMP administered to the patient. Study center personnel and the delegated monitor accounted for all IMP received at the study center, administered to the patient, unused or expired IMP, and for appropriate destruction. Certificates of delivery, destruction and return were to be signed and stored in the Investigator binder.

There were no rescue medications planned for this trial as treatment with an anti-sickling agent

that had not been stable for 3 months before enrollment was not allowed.

The study could have been stopped if, in the judgement of AstraZeneca, study patients were placed at undue risk because of clinically significant findings that:

- Were assessed as causally related to the study treatment.
- Were not considered to be consistent with continuation of the study.

At any time, patients' parents/guardians/legal representatives were free to withdraw the participating child from the study, without prejudice to further treatment. A patient's parents/guardians/legal representatives who decided to withdraw the participating child from the study were always asked about the reason(s) and the presence of any AEs. If possible, the patient was to be seen and assessed by an Investigator(s). The Investigator was to follow-up AEs outside of the clinical study. If a patient withdrew from participation in the study, then his/her enrolment code could not be reused.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up had to be recorded in the eCRF.

Patients received a single dose. None of the patients were discontinued due to an AE.

Study Endpoints

The primary endpoint of the trial was 'observed plasma concentrations as well as PK parameters obtained using a population PK analysis approach, e.g., CL/F (oral clearance), C_{max}, and AUC.

The endpoints were discussed with the FDA prior to the conduct of the study. The FDA detailed the requirements for the study in a written request on June 21, 2019. The sponsor and FDA were in agreement.

No statistical comparisons were planned for the study. All endpoints were evaluated using descriptive statistics.

The PK of ticagrelor and its active metabolite in pediatric patients with SCD aged 0 to <24 months were to be characterized using population PK methodology. The PK was also described by presenting the observed plasma concentrations of ticagrelor and its active metabolite for all individuals, as well as corresponding descriptive statistics per dose- and age groups. Both individual and mean plasma concentrations, with mean taken over observations obtained at a particular time point, were presented graphically. The potential impact of weight, age, and other demographic characteristics on the PK of ticagrelor and its active metabolite were evaluated using population PK methodology.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs and SAEs by preferred term and system organ class were presented using descriptive statistics. For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable were presented. Quantitative variables were summarized using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values. Where appropriate, assessments were summarized by visit. The number of patients screened and included in the Safety analysis and PK analysis were summarized. Demographic and baseline characteristics were summarized and listed for the PK and Safety analysis set.

Acceptability/palatability measures were summarized descriptively.

The above-described methods were appropriate for the trial.

There was no limitation in the primary endpoint of the study.

The secondary endpoints were 1. the observed plasma concentrations as well as PK parameters obtained using a population PK analysis approach, eg C_{max} and AUC and 2. the observer assessment of acceptability and palatability.

The variables corresponding to the secondary objective of assessing the PK properties of the active metabolite were the same as for the primary objective, except for CL/F. For the active metabolite and ticagrelor, area under the plasma concentration-time curve (AUC) was calculated and C_{max} values were derived from observed concentrations.

Acceptability and palatability data
An observer's assessment of the patient's behavior, including willingness to swallow, were performed directly after the patient had been administered a single dose of study treatment on Day 1 (Visit 2). Willingness to swallow was assessed and graded by the following 4 categories:

1. Swallowed without a problem.
2. Some resistance but did swallow.
3. Spat out some/all of the medication.
4. Vomited up the medication.

Negative response to palatability was assessed through the observation of any behavior when the study treatment was given to the patient and recorded as a binary outcome (ie, yes/no). If a negative response was observed, a series of follow-up questions were to be asked to determine the nature of the negative response; these were also to be recorded in a binary fashion or as free text.

Statistical Analysis Plan

Given this was primarily a PK study, no statistical comparisons were planned for the study. All endpoints were evaluated using descriptive statistics. The sponsor and FDA were in agreement.

All patients who received at least 1 dose of ticagrelor and provide at least 1 post-dose analyzable plasma sample for PK analysis will be included in the PK analysis set. Patients with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK may be excluded from the PK analysis set.

All patients who received at least 1 dose of ticagrelor and provide at least 1 post-dose analyzable plasma sample for PK analysis will be included in the PK analysis set.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that the study was performed in compliance with Good Clinical Practice, including the archiving of essential documents, and oversight by an IRB/IEC. Informed consent was documented for each patient (parent/guardian/legal representative).

Financial Disclosure:

The applicant has adequately disclosed financial interests/ arrangements with clinical investigators as recommended in the guidance for industry. There are no financial interests or arrangements to disclose by the investigators. (See Section 13.2 for further detail).

Patient Disposition

The disposition of the patients in this study is summarized in Table 8.

Twenty-three patients were enrolled, 1 (4.3%) patient was withdrawn by their parent/guardian and 1 (4.3%) patient failed screening. Twenty-one patients (2 patients aged <6 months, 6 patients aged 6 months to <12 months and 13 patients 12 months to <24 months) were dosed, and all completed the study. Nineteen patients received a single 0.2 mg/kg oral dose of ticagrelor and 2 patients received a single 0.1 mg/kg oral dose of ticagrelor.

Table 8 Patient Disposition (HESTIA4)

	Number (%) of patients				
	Ticagrelor single oral 0.1 mg/kg dose	Ticagrelor single oral 0.2 mg/kg dose			Total
	<6 months old	6 to <12 months old	12 to <24 months old	Total	
Patients enrolled[a]					23
Patients who received treatment	2 (100.0)	6 (100.0)	13 (86.7)	19 (90.5)	21 (91.3)
Patients who received treatment after re-screening	0	0	2 (13.3)	2 (9.5)	2 (8.7)
Patients who did not receive treatment	0	0	2 (13.3)	2 (9.5)	2 (8.7)
Withdrawal by parent/guardian	0	0	1 (6.7)	1 (4.8)	1 (4.3)
Screen failure	0	0	1 (6.7)	1 (4.8)	1 (4.3)
Patients who completed study	2 (100.0)	6 (100.0)	13 (86.7)	19 (90.5)	21 (91.3)
Patients withdrawn from study	0	0	0	0	0

[a] Informed consent received.
Percentages are calculated out of total number of patients in each treatment and age combination group.
Rescreened patients are counted only once in the enrolled row.
Source: Table 11.1.1.

Source: Applicant submission

Protocol Violations/Deviations

Individual patients with important protocol deviations are summarized in Table 9.

Two patients had an important protocol deviation:

- Patient (b) (6) (12-months-old male), albumin was not measured at screening (exclusion criterion 6).
- Patient (b) (6) (20-months-old male), the 7-day window for laboratory assessments was incorrectly calculated from the date of the laboratory report instead of the date of sample collection.

Table 9 Protocol Deviations (HESTIA4)

	Number (%) of patients				
	Ticagrelor single oral 0.1 mg/kg dose	Ticagrelor single oral 0.2 mg/kg dose			Total
Important protocol deviations[a]	< 6 months old (N=2)	6 to < 12 months old (N=6)	12 to < 24 months old (N=13)	Total (N=19)	(N=21)
Number of patients with at least 1 important deviation	0	0	2 (15.4)	2 (10.5)	2 (9.5)
Any visit missed or not performed according to CSP that resulted in missing critical data	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Key study visit assessment are missed or not conducted according to CSP	0	0	1 (7.7)	1 (5.3)	1 (4.8)

N Number of patients in treatment and age combination group.
[a] Important deviations before the start of treatment and during treatment.
Note that the same patient may have had more than 1 important protocol deviation.
Percentages are calculated out of total number of patients in each treatment and age combination group.

[Source: ASTRAZENECA\TICAGRELOR\NYA13933\BIOSTATISTICS\PRODUCTION\TABLES\DD200.SAS] (b) (4) 11JUL2019

Source: Applicant submission

The number and type of protocol violations is limited and not likely to have an impact on the study results.

Table of Demographic Characteristics

The demographic and key baseline characteristics of study patients are summarized in Table 10.

Of the 21 patients receiving ticagrelor; 2 patients were aged <6 months, 6 patients were aged 6 months to <12 months and 13 patients were aged 12 months to <24 months. Eleven (52.4%) patients were male and 10 (47.6%) patients were female; 7 (33.3%) patients were white and 14 (66.7%) were black or African American.

Table 10 Demographic Characteristics (HESTIA4)

		Ticagrelor single oral 0.1 mg/kg dose	Ticagrelor single oral 0.2 mg/kg dose			Total
		<6 months old	6 to <12 months old	12 to <24 months old	Total	
Demographic characteristics		(N=2)	(N=6)	(N=13)	(N=19)	(N=21)
Age (months)	n	2	6	13	19	21
	Mean	3.5	9.0	16.2	13.9	12.9
	SD	0.71	1.26	3.00	4.25	5.11
	Median	3.5	9.5	16.0	13.0	13.0
	Min	3	7	12	7	3
	Max	4	10	21	21	21
Sex n (%)	Male	1 (50.0)	2 (33.3)	8 (61.5)	10 (52.6)	11 (52.4)
	Female	1 (50.0)	4 (66.7)	5 (38.5)	9 (47.4)	10 (47.6)
Race n (%)	White	2 (100.0)	0	5 (38.5)	5 (26.3)	7 (33.3)
	Black or African American	0	6 (100.0)	8 (61.5)	14 (73.7)	14 (66.7)
	Asian	0	0	0	0	0
	Native Hawaiian Or Other Pacific Islander	0	0	0	0	0
	American Indian Or Alaska Native	0	0	0	0	0
Ethnicity n (%)	Hispanic or Latino	0	0	0	0	0
	Not Hispanic or Latino	2 (100.0)	6 (100.0)	13 (100.0)	19 (100.0)	21 (100.0)

The number of patients with data (ie, Total row) for each characteristic and row was used as the denominator for calculating percentages.
Age is collected at date of informed consent.
Max: maximum; Min: minimum; N: number of patients in treatment and age combination group; n: number of patients included in the analysis; SD: standard deviation.
Source: Table 11.1.4.

Source: Applicant submission

Additional patient characteristics are included in Table 11 (height and body weight).

Table 11 Demographic Characteristics - Height and Weight (HESTIA4)

		Ticagrelor single oral 0.1 mg/kg dose	Ticagrelor single oral 0.2 mg/kg dose			Total
		< 6 months old	6 to < 12 months old	12 to < 24 months old	Total	
Patient characteristics		(N=2)	(N=6)	(N=13)	(N=19)	(N=21)
Height (cm)	n	2	6	13	19	21
	Mean	66.5	69.8	80.3	77.0	76.0
	SD	4.95	4.49	4.57	6.67	7.16
	Median	66.5	69.0	79.0	77.0	77.0
	Min	63	66	74	66	63
	Max	70	78	88	88	88
Weight (kg)	n	2	6	13	19	21
	Mean	7.25	8.45	10.57	9.90	9.65
	SD	0.495	0.599	1.286	1.492	1.628
	Median	7.25	8.55	10.10	9.90	9.90
	Min	6.9	7.4	8.0	7.4	6.9
	Max	7.6	9.0	13.3	13.3	13.3

Max Maximum. Min Minimum. N Number of patients in treatment and age combination group. n Number of patients included in the analysis. SD Standard deviation.

[Source: ASTRAZENECA\TICAGRELOR\NYA13933\BIOSTATISTICS\PRODUCTION\TABLES\DM201.SAS] (b) (4) 11JUL2019

Source: Applicant submission

The demographic and baseline characteristics of the patients were considered appropriate to achieve the objectives of the study.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Sickle cell disease characteristics summarized in Table 12. The SCD genotype was HbSS for all patients and the duration since confirmation of the disease ranged from 0.1 month to 16.2 months. Sickle cell disease characteristics were recorded as: dactylitis or hand-foot syndrome in 4 (19.0%) patients, splenic sequestration in 1 (4.8%) patient, and other in 2 (9.5%) patients. There were no symptoms recorded in 14 (66.7%) patients.

Table 12 SCD Characteristics at Baseline (HESTIA4)

Disease characteristics		Ticagrelor single oral 0.1 mg/kg dose < 6 months old (N=2)		Ticagrelor single oral 0.2 mg/kg dose 6 to < 12 months old (N=6)		12 to < 24 months old (N=13)		Total (N=19)		Total (N=21)	
Sickle Cell Disease Genotype n (%)	HbSS	2	(100.0)	6	(100.0)	13	(100.0)	19	(100.0)	21	(100.0)
	HbSS° Thalassemia	0		0		0		0		0	
	Total	2		6		13		19		21	
Sickle Cell Disease Characteristics n (%)	Dactylitis or Hand-foot Syndrome	0		2	(33.3)	2	(15.4)	4	(21.1)	4	(19.0)
	Splenic Sequestration	0		0		1	(7.7)	1	(5.3)	1	(4.8)
	Other	0		2	(33.3)	0		2	(10.5)	2	(9.5)
	No Symptoms	2	(100.0)	2	(33.3)	10	(76.9)	12	(63.2)	14	(66.7)
	Total	2		6		13		19		21	
Duration of disease (months)	n	2		6		13		19		21	
	Mean	2.96		3.55		8.05		6.63		6.28	
	SD	1.022		4.537		5.360		5.432		5.275	
	Median	2.96		1.15		9.99		7.16		3.68	
	Min	2.2		0.1		0.3		0.1		0.1	
	Max	3.7		9.6		16.2		16.2		16.2	

HbSS Homozygous sickle cell anaemia. HbSS° Sickle beta-zero-thalassaemia. Max Maximum. Min Minimum. N Number of patients in treatment and age combination group. n Number of patients included in the analysis. SD Standard deviation.
The number of patients with data (i.e. 'Total' row) for each characteristic will be used as the denominator for calculating percentages.
A patient can have more than one sickle cell disease characteristic.
Duration of disease is calculated relative to date of the first dose.

[Source: ASTRAZENECA\TICAGRELOR\NYA13933\BIOSTATISTICS\PRODUCTION\TABLES\DM203.SAS] (b) (4) 11JUL2019

Source: Applicant submission

Relevant past medical histories are summarized in Table 13. At the preferred term (PT) level, the most common relevant medical history was pyrexia in 5 (23.8%) patients (1 [16.7%] patient aged 6 months to <12 months and 4 [30.8%] patients 12 months to <24 months). Anemia, gastroenteritis, pneumonia, upper respiratory tract infection, and dactylitis were each recorded in 2 (9.5%) patients. All other relevant medical histories were each recorded in 1 patient. One patient (Patient (b) (6); 13-months-old female) had a surgical history of osteomyelitis (surgical drainage on right foot and right hand).

Table 13 Relevant Past Medical History at Baseline (HESTIA4)

	Number (%) of patients[b]				
	Ticagrelor single oral 0.1 mg/kg dose	Ticagrelor single oral 0.2 mg/kg dose			Total
System organ class/ Preferred term[a]	< 6 months old (N=2)	6 to < 12 months old (N=6)	12 to < 24 months old (N=13)	Total (N=19)	(N=21)
Blood and lymphatic system disorders	0	0	2 (15.4)	2 (10.5)	2 (9.5)
Anaemia	0	0	2 (15.4)	2 (10.5)	2 (9.5)
Congenital, familial and genetic disorders	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Ichthyosis	0	0	1 (7.7)	1 (5.3)	1 (4.8)
General disorders and administration site conditions	0	1 (16.7)	4 (30.8)	5 (26.3)	5 (23.8)
Pyrexia	0	1 (16.7)	4 (30.8)	5 (26.3)	5 (23.8)
Hepatobiliary disorders	0	1 (16.7)	1 (7.7)	2 (10.5)	2 (9.5)
Hepatomegaly	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Jaundice	0	1 (16.7)	0	1 (5.3)	1 (4.8)
Infections and infestations	0	2 (33.3)	6 (46.2)	8 (42.1)	8 (38.1)
Ear infection	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Gastroenteritis	0	0	2 (15.4)	2 (10.5)	2 (9.5)
Osteomyelitis	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Pneumonia	0	1 (16.7)	1 (7.7)	2 (10.5)	2 (9.5)
Rhinitis	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Tonsillitis	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Upper respiratory tract infection	0	0	2 (15.4)	2 (10.5)	2 (9.5)

	Number (%) of patients[b]				
	Ticagrelor single oral 0.1 mg/kg dose	Ticagrelor single oral 0.2 mg/kg dose			Total
System organ class/ Preferred term[a]	< 6 months old (N=2)	6 to < 12 months old (N=6)	12 to < 24 months old (N=13)	Total (N=19)	(N=21)
Infections and infestations	0	1 (16.7)	0	1 (5.3)	1 (4.8)
Viral upper respiratory tract infection	0	1 (16.7)	0	1 (5.3)	1 (4.8)
Injury, poisoning and procedural complications	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Wound	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Musculoskeletal and connective tissue disorders	0	0	2 (15.4)	2 (10.5)	2 (9.5)
Dactylitis	0	0	2 (15.4)	2 (10.5)	2 (9.5)
Respiratory, thoracic and mediastinal disorders	0	0	2 (15.4)	2 (10.5)	2 (9.5)
Rhinitis allergic	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Rhinorrhoea	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Skin and subcutaneous tissue disorders	0	1 (16.7)	0	1 (5.3)	1 (4.8)
Eczema	0	1 (16.7)	0	1 (5.3)	1 (4.8)
Vascular disorders	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Pallor	0	0	1 (7.7)	1 (5.3)	1 (4.8)

N Number of patients in treatment and age combination group.
[a] Number (%) of patients are sorted by international order for System Organ Class (SOC) and alphabetically for Preferred Term (PT). A patient can have one or more PTs reported under a given SOC.
[b] Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than 1 preferred term are counted once in each of those preferred terms.
Percentages are calculated out of total number of patients in each treatment and age combination group.
Verbatim term is used when the PT is not coded.
MedDRA version 20.1

[Source: ASTRAZENECA\TICAGRELOR\NYA13933\BIOSTATISTICS\PRODUCTION\TABLES\MH200.SAS] (b) (4) 11JUL2019

Source: Applicant submission

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant medications were administered during the study to 20 (95.2%) patients:

2 (100%) patients aged <6 months, 6 (100%) patients aged 6 months to <12 months and 12 (92.3%) patients aged 12 to <24 months. Concomitant medications, by Anatomical Therapeutic Classification, administered to more than 1 patient were:

- Vitamin D and analogues (1 [50%] patient aged <6 months and 6 [46.2%] patients aged 12 months to <24 months).
- Folic acid and derivatives (1 [50%] patient aged <6 months, 5 [83.3%] patients aged 6 months to <12 months and 10 [76.9%] patients 12 months to <24 months).
- Penicillins with extended spectrum (2 [100%] patients aged <6 months and 9 [69.2%] patients aged 12 months to <24 months).
- Beta-lactamase sensitive penicillins (5 [83.3%] patients aged 6 months to <12 months and 3 [23.1%] patients aged 12 to <24 months).
- Other antineoplastic agents (hydroxycarbamide) (3 [23.1%] patients aged 12 months to <24 months).
- Anilides (2 [33.3%] patients 6 months to <12 months and 2 [15.4%] patients aged 12 months to <24 months old).
- Biguanides (3 [50%] patients aged 6 months to <12 months).
- Substituted alkylamines (2 [33.3%] patients aged 6 months to <12 months old).

In the source document for concomitant medications, hydromol is listed for Patient (b) (6), the details were not entered into the database or reported in the data listing.

There were no rescue medications planned for this study.

Efficacy Results – Primary Endpoint

The primary endpoint, which addresses the PK properties of ticagrelor after administration of a single oral dose, was the observed plasma concentration of ticagrelor and the PK parameters obtained partly from observed plasma concentrations and partly using a population PK approach.

In the 19 patients receiving 0.2 mg/kg ticagrelor, the maximum plasma concentration of ticagrelor was generally measured at 1 hour or 2 hours post-dose and the plasma concentrations decreased at the 4- and 6-hour sample timepoints.

The maximum geometric mean plasma concentration of ticagrelor after oral administration of 0.2 mg/kg ticagrelor (21.82 ng/mL) occurred at the 2-hour sample timepoint. In the 2 patients <6 months old receiving 0.1 mg/kg ticagrelor there was no 1-hour sample for 1 patient. The maximum plasma concentration of ticagrelor was measured at the first sample timepoint (1 or 2 hours, respectively) and plasma concentrations declined at each of the subsequent sample

timepoints. Mean values were not calculated. At 2 hours post-dose ticagrelor plasma concentrations were 17.6 and 28.1 ng/mL.

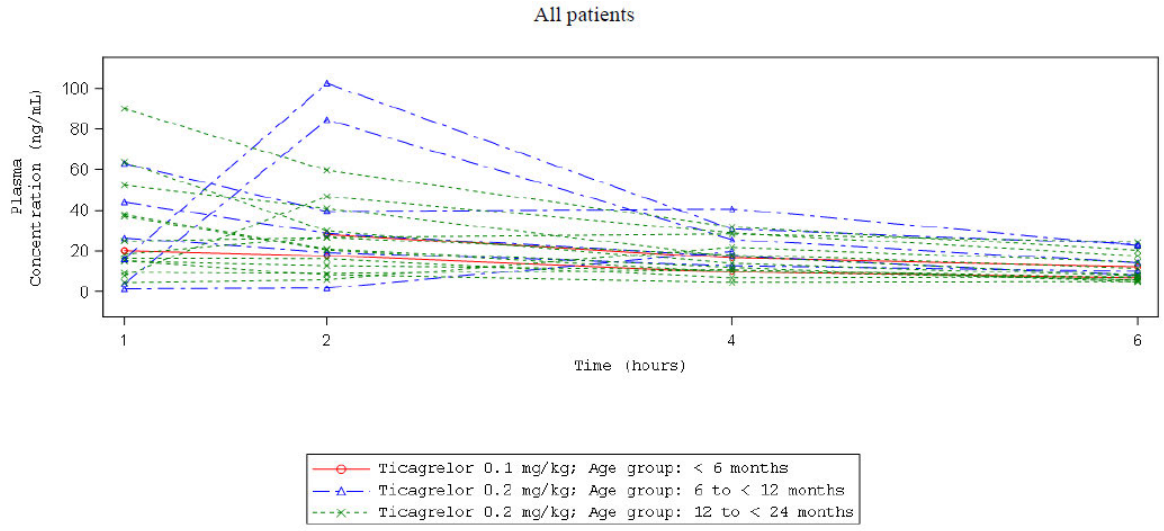
There was no concentration below lower limit of quantification reported (ie, <1.0 ng/mL).

Individual plasma concentrations of ticagrelor versus time are presented on a linear scale in Figure 2 and a summary of the plasma concentrations are presented in Table 14. A summary of the PK parameters Cmax and AUC_{0-6h} calculated for ticagrelor are presented in Table 15.

Following administration of 0.2 mg/kg ticagrelor, geometric mean plasma C_{max} and AUC_{0-6h} values were calculated as 34.44 ng/mL and 112.39 ng.h/mL, respectively. Following administration of 0.1 mg/kg ticagrelor, geometric mean plasma C_{max} and AUC_{0-6h} values were calculated as 23.80 ng/mL and 87.22 ng.h/mL, respectively.

The C_{max} and AUC_{0-6h} values were similar following administration of 0.2 mg/kg ticagrelor in patients aged 6 months to <12 months and 12 months to <24 months (C_{max}: 48.23 ng/mL and 29.48 ng/mL, and AUC_{0-6h}: 141.68 ng.h/mL and 101.00 ng.h/mL, respectively).

Figure 2 Individual Plasma Concentrations (ng/mL) versus Time Profiles of Ticagrelor (linear scale) (PK Analysis Set) (HESTIA4)



Patients received a single dose of ticagrelor on Day 1.
1.0 ng/mL = lower limit of quantification.
Source: Figure 11.2.1.1.1.

Source: Applicant submission

Table 14 Summary of Plasma Concentrations (ng/mL) of ticagrelor (PK Analysis Set) (HESTIA4)

		Planned time after dose intake (hours)			
Group	**Summary statistic**	**1**	**2**	**4**	**6**
All patients (N=21)	n	20	21	21	20
	Concentration < LLOQ	0	0	0	0
	Geometric mean	18.59	21.86	16.12	10.25
	Geometric CV (%)	147.75	118.47	59.75	58.23
	Arithmetic mean	28.33	30.72	18.44	11.80
	SD	23.807	25.376	9.474	6.561
	Median	19.35	26.66	17.17	9.09
	Min	1.2	1.7	4.6	4.9
	Max	90.0	102.5	40.7	24.4
Ticagrelor	n	1	2	2	2
0.1 mg, <6 (N=2)	Concentration < LLOQ	0	0	0	0
	Geometric mean	NC	NC	NC	NC
	Geometric CV (%)	NC	NC	NC	NC
	Arithmetic mean	NC	NC	NC	NC
	SD	NC	NC	NC	NC
	Median	NC	NC	NC	NC
	Min	NC	17.6	9.6	6.7
	Max	NC	28.1	16.5	12.2
Ticagrelor	n	19	19	19	18
0.2 mg, total (N=19)	Concentration < LLOQ	0	0	0	0
	Geometric mean	18.51	21.82	16.54	10.39
	Geometric CV (%)	154.70	127.79	61.78	60.68
	Arithmetic mean	28.76	31.55	19.01	12.06
	SD	24.380	26.547	9.736	6.817
	Median	18.53	26.66	17.40	9.09
	Min	1.2	1.7	4.6	4.9
	Max	90.0	102.5	40.7	24.4

Table 15 Summary of Plasma Pharmacokinetic Parameters of Ticagrelor (PK Analysis Set) (HESTIA4)

		Pharmacokinetic parameters	
Group	**Summary statistic**	**AUC (ng.h/mL)**	**C_{max} (ng/mL)**
All patients (N=21)	n	21	21
	Geometric mean	109.71	33.25
	Geometric CV (%)	50.59	71.67
	Arithmetic mean	122.06	40.48
	SD	57.364	26.602
	Median	109.28	28.36
	Min	52.0	10.8
	Max	243.8	102.5
Ticagrelor	n	2	2
0.1 mg, <6 (N=2)	Geometric mean	87.22	23.80
	Geometric CV (%)	32.72	23.78
	Arithmetic mean	89.45	24.13
	SD	28.053	5.607
	Median	89.45	24.13
	Min	69.6	20.2
	Max	109.3	28.1
Ticagrelor	n	19	19
0.2 mg, total (N=19)	Geometric mean	112.39	34.44
	Geometric CV (%)	52.21	74.75
	Arithmetic mean	125.49	42.20
	SD	59.008	27.418
	Median	115.33	37.02
	Min	52.0	10.8
	Max	243.8	102.5

Source: Applicant submission

The applicant and the FDA are in agreement with the primary efficacy variable analysis.

Efficacy Results – Secondary and other relevant endpoints

In the 19 patients receiving 0.2 mg/kg ticagrelor the plasma concentrations were lower for the active metabolite than for ticagrelor. The maximum plasma concentration of the metabolite was generally measured at the later sample timepoints (4 or 6 hours) compared with the maximum plasma concentration of ticagrelor (1 or 2 hours).

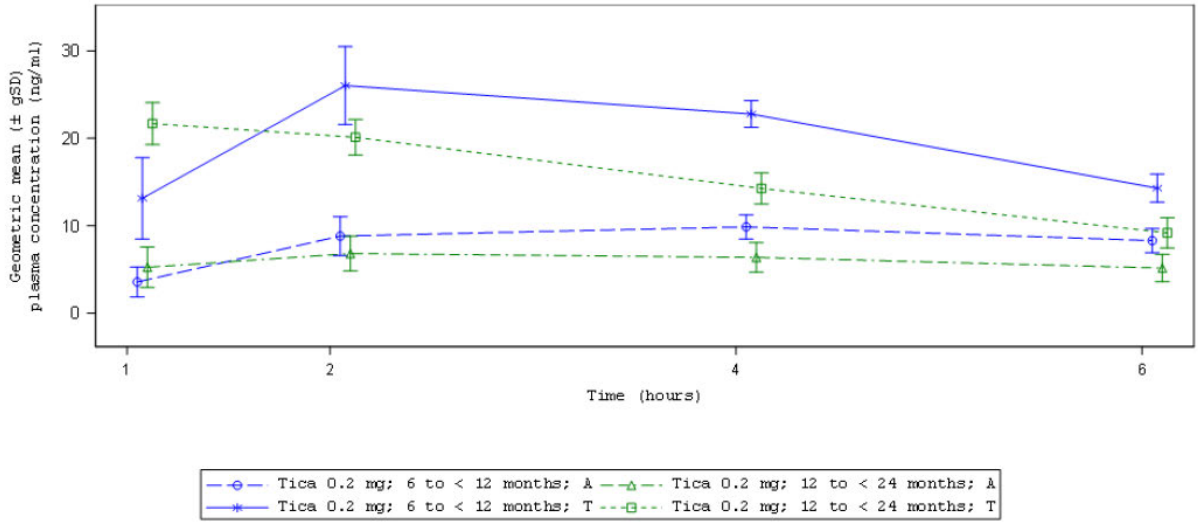
The maximum geometric mean plasma concentration of the active metabolite after oral administration of 0.2 mg/kg ticagrelor occurred at the 2-hour (7.4 ng/mL) sample timepoint. The geometric mean plasma concentration-time profiles for ticagrelor and the active metabolite are presented in Figure 3.

In the 2 patients <6 months old receiving 0.1 mg/kg ticagrelor, there was no 1-hour sample for 1 patient. The maximum plasma concentration of active metabolite occurred at the 2-hour sample time for both patients (5.9 ng/mL and 8.1 ng/mL). Mean values were not calculated. Individual plasma concentrations of active metabolite versus time are presented on a linear scale in Figure 4 and a summary of the plasma concentrations are presented in Table 16.

A summary of the PK parameters C_{max} and AUC_{0-6h} calculated for active metabolite are presented in Table 17. Following administration of 0.2 mg/kg ticagrelor, geometric mean plasma C_{max} and AUC_{0-6h} values were calculated as 9.17 ng/mL and 34.97 ng.h/mL, respectively. Following administration of 0.1 mg/kg ticagrelor, geometric mean plasma C_{max} and AUC_{0-6h} values were calculated as 6.89 ng/mL and 29.76 ng.h/mL, respectively.

The C_{max} and AUC_{0-6h} values calculated for active metabolite were similar following administration of 0.2 mg/kg ticagrelor in patients aged 6 months to <12 months and 12 months to <24 months (C_{max}: 11.5 ng/mL and 8.26 ng/mL, and AUC_{0-6h}: and 43.66 ng.h/mL and 31.56 ng.h/mL, respectively).

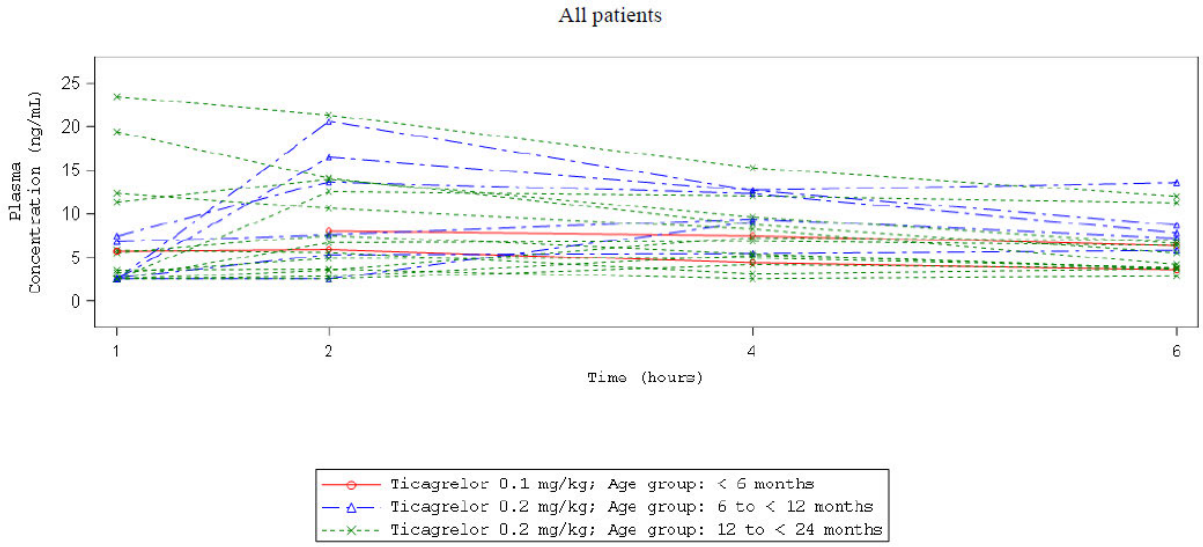
Figure 3 Geometric Mean Plasma Concentration (ng/mL) versus Time Profiles of ticagrelor and Active Metabolite (linear scale) (PK Analysis Set) (HESTIA4)



Patients received a single oral dose of ticagrelor on Day 1.
Ticagrelor assay lower limit of quantification was 1.00 ng/mL.
Active metabolite assay lower limit of quantification was 2.50 ng/mL.
A: active metabolite; T: ticagrelor; gSD; geometric standard deviation.
Source: Figure 11.2.1.5.

Source: Applicant submission

Figure 4 Individual Plasma Concentrations (ng/mL) versus Time Profiles of Active Metabolite (Linear Scale) (PK Analysis Set) (HESTIA4)



Patients received a single dose of ticagrelor on Day 1.
2.50 ng/mL = lower limit of quantification.
Source: Figure 11.2.1.1.2.

Source: Applicant submission

Table 16 Summary of Plasma Concentrations (ng/mL) of Active Metabolite (PK Analysis Set) (HESTIA4)

		Planned time after dose intake (hours)			
Group	**Summary statistic**	**1**	**2**	**4**	**6**
All patients (N=21)	n	20	21	21	20
	Concentration < LLOQ	8	2	1	0
	Geometric mean	4.70	7.35	7.16	5.77
	Geometric CV (%)	85.91	76.39	52.08	47.77
	Arithmetic mean	6.36	9.04	7.95	6.38
	SD	5.969	5.804	3.550	3.059
	Median	3.40	7.57	7.54	6.07
	Min	2.5	2.5	2.5	2.8
	Max	23.5	21.3	15.3	13.6
Ticagrelor	n	1	2	2	2
0.1 mg, <6(N=2)	Concentration < LLOQ	0	0	0	0
	Geometric mean	NC	NC	NC	NC
	Geometric CV (%)	NC	NC	NC	NC
	Arithmetic mean	NC	NC	NC	NC
	SD	NC	NC	NC	NC
	Median	NC	NC	NC	NC
	Min	NC	5.9	4.4	3.6
	Max	NC	8.1	7.5	6.3
Ticagrelor	n	19	19	19	18
0.2 mg, total (N=19)	Concentration < LLOQ	8	2	1	0
	Geometric mean	4.65	7.40	7.33	5.89
	Geometric CV (%)	88.79	81.31	53.57	49.02
	Arithmetic mean	6.40	9.26	8.17	6.53
	SD	6.130	6.065	3.638	3.158
	Median	3.26	7.57	8.29	6.09
	Min	2.5	2.5	2.5	2.8
	Max	23.5	21.3	15.3	13.6

Source: Applicant submission

Table 17 Summary of Plasma Pharmacokinetic Parameters of Active Metabolite (PK Analysis Set) (HESTIA4)

		Pharmacokinetic parameters	
Group	**Summary statistic**	**AUC (ng.h/mL)**	**C_{max} (ng/mL)**
All patients (N=21)	n	21	21
	Geometric mean	34.44	8.93
	Geometric CV (%)	55.80	58.76
	Arithmetic mean	39.12	10.30
	SD	20.562	5.772
	Median	31.44	8.07
	Min	12.4	3.7
	Max	91.5	23.5
Ticagrelor	n	2	2
0.1 mg, < 6 (N=2)	Geometric mean	29.76	6.89
	Geometric CV (%)	22.84	22.55
	Arithmetic mean	30.13	6.98
	SD	6.737	1.541
	Median	30.13	6.98
	Min	25.4	5.9
	Max	34.9	8.1
Ticagrelor	n	19	19
0.2 mg, total (N=19)	Geometric mean	34.97	9.17
	Geometric CV (%)	58.67	61.25
	Arithmetic mean	40.07	10.64
	SD	21.385	5.961
	Median	31.44	9.12
	Min	12.4	3.7
	Max	91.5	23.5

Patients received a single dose of ticagrelor on Day 1.
AUC: area under the plasma concentration-time curve from zero to 6 hours; C_{max}: maximum observed plasma concentration; CV: coefficient of variation; Max: maximum; Min: minimum; N: number of patients in treatment and age combination group; n: number of patients included in the analysis; SD: standard deviation.
Source: Table 11.2.2.2

Source: Applicant submission

Acceptability and palatability of ticagrelor
There was some resistance to swallow the medication (0.2 mg/kg ticagrelor) in 3 patients; they turned their head to reject intake of the medication but did swallow the medication. One

patient (Patient [redacted], 10-month-old female) turned her head and twisted her face or mouth to reject intake of the medication (0.2 mg/kg ticagrelor) and spat out some of the medication.

Dose/Dose Response

N/A

Durability of Response

N/A

Persistence of Effect

N/A

Additional Analyses Conducted on the Individual Trial

N/A

6.2 HESTIA3

6.2.1 Study Design

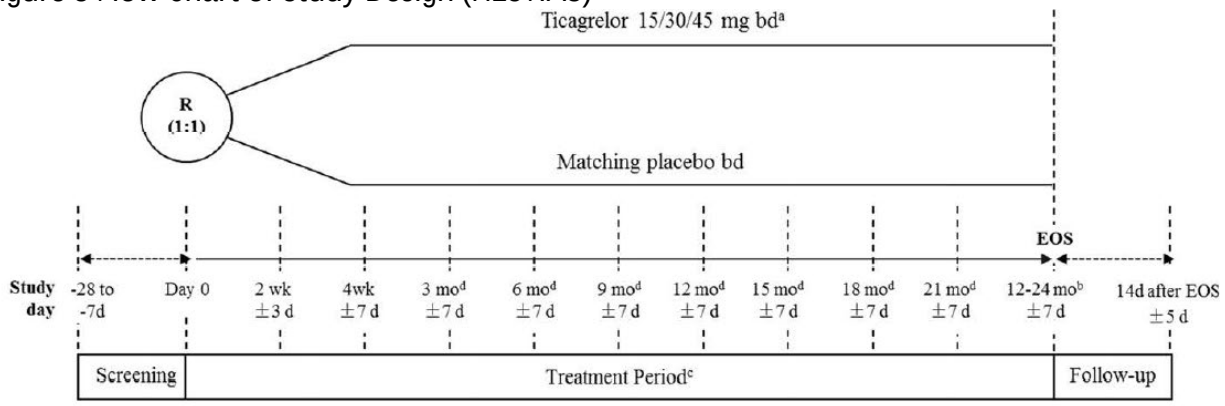
Overview and Objective

D5136C00009: A Randomized, Double-Blind, Parallel-Group, Multicenter, Phase III Study to Evaluate the Effect of Ticagrelor versus Placebo in Reducing the Rate of Vaso-Occlusive Crises in Pediatric Patients with Sickle Cell Disease (HESTIA3)

The trial was intended to evaluate the efficacy and the long-term safety and tolerability of ticagrelor vs. placebo in the treatment of pediatric patients aged 2 years to <18 years. The trial also evaluated population PK parameters, exposure (AUC), and the effect of ticagrelor on platelet aggregation.

Trial Design

Figure 5 Flow Chart of Study Design (HESTIA3)



[a] Patients randomised to ticagrelor will receive doses based on weight band (at Screening): ≥ 12 to ≤ 24 kg = 15 mg, > 24 to ≤ 48 kg = 30 mg, > 48 kg = 45 mg.
[b] EOS = Patients were to be followed to a common study end date defined as 12 months after the last patient is randomised, or up to 24 months.
[c] See Table 3 for assessments during site visits and Table 4 for telephone visits that occurred monthly after Week 4 between site visits.
[d] Interval was not to be more than 100 days to ensure tablet supply for all days.
NB. Only on-site visits are shown.
bd, Twice daily; d, Day; EOS, End of study; mo, Month; R, Randomisation; wk, Week.

Source: Applicant submission

This was an international, multi-center, double-blind, randomized, parallel-group, placebo-controlled Phase III study to evaluate the effect of ticagrelor versus placebo in reducing the rate of VOC events in pediatric patients with SCD. Patients were monitored for occurrence of VOC events and other acute SCD complications. Patients received standard of care for SCD adjusted to the individual patient at the discretion of the Investigator. The study drug was given on the background of standard of care for SCD. In the treatment period, patients were followed for up to 24 months or until a common study end date (CSED) was reached, defined as 12 months after the last patient was randomized.

There were no unusual features in the trial design. The design was fit for the purpose of the study goals. Placebo-controlled trials are useful in establishing the efficacy and safety of drugs for the treatment of sickle cell disease.

The study was conducted across 16 countries at a total of 53 sites: Kenya (5), India (6), Uganda (2), Egypt (6), Lebanon (2), Ghana (2), South Africa (2), Tanzania (1), UK (4), Turkey (3), Spain (3), Italy (3), Belgium (2), Greece (1), Brazil (4), and the USA (7). There are many barriers to care in undeveloped countries that are not common in the United States. The accessibility to medicine, whether pain control or a disease modifying agent may be difficult to obtain. The access to a medical facility, especially if in a rural area, or an area that has underdeveloped

public transportation, may also be a challenge. These factors may affect results and may not necessarily allow results to be applicable to the U.S. population.

Placebo was agreed upon by the FDA as a control group because patients were permitted to continue their baseline anti-SCD therapy (hydroxyurea). Placebo is a useful comparator because it allows a clear observation of the treatment effect and safety profile.

Patients diagnosed with HbSS or HbS/β^0 were eligible. Patients with clinically milder variants (eg, sickle cell-hemoglobin C [HbSC]) were not eligible.

The target study population includes male or female pediatric patients aged ≥2 to <18 years and body weight ≥ 12 kg diagnosed with HbSS or HbS/β^0 who have experienced at least 2 VOCs (painful crisis and/or ACS) in the 12 months prior to visit 1. Patients treated with hydroxyurea must be on a stable dose for 3 months before screening.

Any of the following were regarded as exclusion criterion for the study:

- TIA, cerebrovascular accident, or conditional/ abnormal findings on transcranial doppler
- Active pathological bleeding or increased risk of bleeding complications
- Hemoglobin <6 g/dL from test performed at screening
- Platelets <100 x10^9/L from test performed at screening
- Undergoing chronic red blood cell transfusions
- Chronic NSAID use (intake >3 days per week that could not be discontinued)
- Chronic treatment with anticoagulants or antiplatelet drugs that could not be discontinued
- Concomitant oral or IV therapy with strong cytochrome P450 3A (CYP3A) inhibitors, or inducers
- Moderate or severe hepatic impairment (ALT >2 x upper limit of normal (ULN), total bili >2 x ULN, albumin <3.5 g/dL, INR >1.4, or symptoms of liver disease (Ascites) from test performed at screening)
- Renal failure requiring dialysis
- Risk for bradycardic events (sick sinus syndrome or second or third-degree AV block) unless already treated with a permanent pacemaker
- Active untreated malaria
- Patients who are pregnant or breastfeeding, planning to become pregnant during the study, or had given birth less than 3 months prior to screening

The ticagrelor PK/PD modelling and simulation work based on the results from HESTIA1 and HESTIA2 studies identifies 15, 30 and 45 mg bd, depending on body weight, as relevant doses in the HESTIA3 study. These doses are predicted to result in a platelet activity measured as $P2Y_{12}$ reaction units ([PRU] as measured by VerifyNow®) of less than 180,

corresponding to >35% platelet inhibition in terms of reduction in PRU assuming a baseline PRU of 280 (which was the baseline PRU observed in HESTIA1, and similar to prasugrel Phase III DOVE study (Heeney MM H. C., 2016).

The predicted platelet inhibition in HESTIA3 is similar to what was observed in the 45 mg twice daily dose group in the HESTIA2 study in young adults, where after 1 week of treatment the mean percentage decrease from baseline PRU was 48% before the morning dose and 81% at 2 hours the dose. The 45 mg twice daily dose was well tolerated and events of bleeding were of the same number and similar compared to the placebo group and the 10 mg twice daily dose groups. Given the reversible mechanism of action for ticagrelor, the level of $P2Y_{12}$ inhibition during ticagrelor treatment is expected to vary within a dosing interval and peak around 2 hours after dosing.

When developing the dosing strategy for this study, the target for platelet inhibition was guided by the results from the recent prasugrel Phase III study in pediatric patients with SCD aged 2 to 17 years, showing insufficient efficacy with a mean PRU of 207 (ie, approximately 20% reduction from baseline) (Jakubowski JA, 2017). The lack of therapeutic benefit with prasugrel may have been related to a too low platelet inhibition (Heeney MM A. M., 2019), and consequently, doses for HESTIA3 were selected to achieve a greater level of platelet inhibition. Moreover, a study with ticlopidine in adolescents and adult patients with SCD showing significant reductions in VOC (Cabannes R, 1984) used doses that generally provide <60% inhibition of platelet aggregation, which provides further support for the platelet inhibition target and the selected doses for the HESTIA3 study.

The doses used in this study were agreeable with the FDA.

Study Treatment is displayed in Table 18.

Table 18 Study Treatment (HESTIA3)

	Ticagrelor	Placebo
Dosage Formulation	Plain, round, biconvex, white/off-white, uncoated, 15mg tablet	Plain, round, biconvex, white/off-white, uncoated, containing no active ingredient
Route of Administration	Oral	Oral
Dosing Instructions	Tablets were taken twice daily in the morning and evening at approximately 12 hour intervals, with or without food.	Tablets were taken twice daily in the morning and evening at approximately 12 hour intervals, with or without food.

	The number of tablets taken was based on body weight at Visit 2: • ≥ 12 to ≤ 24 kg body weight: 15 mg – 1 tablet of ticagrelor 15 mg twice daily • > 24 to ≤ 48 kg body weight: 30 mg – 2 tablets of ticagrelor 15 mg twice daily • > 48 kg body weight: 45 mg – 3 tablets of ticagrelor 15 mg	The number of tablets taken was based on body weight at Visit 2: • ≥ 12 to ≤ 24 kg body weight: 1 tablet of placebo to match ticagrelor 15 mg twice daily • > 24 to ≤ 48 kg body weight: 2 tablets of placebo to match ticagrelor 15mg twice daily • > 48 kg body weight: 3 tablets of placebo to match ticagrelor 15 mg twice daily
Packaging and Labeling	Study treatment was provided in high-density polyethylene bottles. Each bottle was labelled in accordance with GMP Annex 13 and per country regulatory requirement	Study treatment was provided in high-density polyethylene bottles. Each bottle was labelled in accordance with GMP Annex 13 and per country regulatory requirement.
Batch Numbers	Ticagrelor 15 mg bottle L009925 L011556 L007378 L013017	Ticagrelor 15 mg placebo bottle L007542 L013018 L010045 L007542/L008177 L011620

Source: Applicant submission

After obtaining informed consent/assent from the caregiver of the potential patient (or the patient, if applicable), the investigator will assign (using the Interactive Voice/Web Response System [IXRS]) the potential patient a unique enrolment number, beginning with 'E + 4-digit site number + 3-digit patient number starting with 501. For example, the first patient at site 9999 would be assigned the patient number: E9999001. This number will be used for identification (ID) throughout the study and will not be used for any other participant. The investigator will then determine patient eligibility and assign the eligible patient a unique randomization code (patient number), by accessing IXRS.

Patients who have not been randomized can be re-enrolled in the study if they meet eligibility criteria at a later date; however, no patient can be re-randomized. Any re-enrolment of patients must be done in consultation of the Sponsor's study physician and any decision must be captured in the patient's medical notes. If a patient withdraws from participation in the study, then his/ her enrolment/ randomization code cannot be reused.

The randomization codes will be computer generated by AstraZeneca R&D and loaded into the IXRS database. Randomization codes will be generated in blocks to ensure approximate balance (1:1) between the 2 treatment arms (ticagrelor or placebo twice daily). Stratification for baseline hydroxyurea use by country will be applied.

For each patient randomized the IXRS will provide the Investigator with a unique kit ID number matching the treatment arm assigned to the patient. Following randomization, the first dose of study drug will be administered to the patient as soon as possible. At randomization and subsequent dispensing visits, the patient should always be provided medication with the kit ID(s) allocated by the IXRS. If a patient receives the incorrect randomized treatment at any time during the study, this must be corrected as soon as discovered after discussing with the study physician.

This is a double-blind study. Ticagrelor and matching ticagrelor placebo tablets were identical in appearance and packaging. The bottles with IPs were labelled with unique ID numbers allocated from the IXRS but did not indicate treatment allocation. There was little potential for unblinding due to differences in appearance in the products or adverse events. The primary endpoint is somewhat susceptible to bias because patients self-report their painful VOCs.

For any patient having a weight gain during the study period clearly exceeding the upper weight limit of the band ($\geq$ 27 kg and $\geq$ 54 kg, respectively), the dose was to be increased according to the next weight band.

In case of a dose increase:

- IxRS generated correct dose based on body weight range entered
- Stop date for the old dose and start date for the new dose were to be recorded in the eCRF
- The patient was to return all unused IP and empty bottles and new IP bottles were to be dispensed
- PK and PD samples were to be taken at the following visit after the adjusted dose had been dispensed.

Patients were to be permanently discontinued from the investigational product (IP) in the following situations:

1. The patient (or caregiver) was at any time free to discontinue treatment or advise the patient to discontinue treatment, without prejudice to further treatment.
2. AE, as judged by Investigator, that with continued treatment would put the patient at undue risk.
3. Severe non-compliance with the CSP, as judged by Investigator and/or AstraZeneca.
4. Severe illness or risk to the patient as judged by the Investigator.

5. Any major bleeding, for bleeding definitions see CSP Section 6.3.8.
6. Repeated minor bleedings not needing medical intervention unless clearly not related to study drug (eg, minor trauma during playing), as judged by the Investigator.
7. For females of childbearing potential, who were sexually active and where effective contraception could not be secured, the study treatment had to be discontinued.
8. In the event of pregnancy, study drug was to be immediately permanently discontinued. The patient was encouraged to continue to be followed in the study according to the study plan.
9. Conditional or Abnormal TCD findings, ie, TAMMV values are ≥ 153 cm/sec using TCDi technique (corresponding to ≥ 170 cm/sec by the non-imaging technique), indicating an increased risk of stroke.
10. Pathological findings on any imaging technique indicating increased risk of ischemic or hemorrhagic stroke.
11. TIA or stroke (ischemic or hemorrhagic).
12. Need for chronic transfusion therapy.
13. Findings indicating impaired liver function and/or coagulopathy
14. Renal failure requiring dialysis.
15. Patients with clinical symptoms of bradyarrhythmia as judged by the Investigator and/or ECG findings of significant sinus pauses or high degree atrioventricular block.
16. Development of proliferative retinopathy.
17. Need for chronic use of NSAIDs, defined as continuous intake > 3 days per week.

At any time, patients were free to discontinue IP, without prejudice to further treatment. A patient that decided to discontinue IP was always to be asked about the reason(s) and the presence of any AEs. Adverse events (AEs) were followed up and all Ips returned by the patient. Patients permanently discontinuing IP were always to be asked to continue the regular visits. It was essential to collect as much data as possible for all patients throughout the study and especially all potential endpoint events. Complete withdrawal from the study (withdrawal of consent) has a direct negative impact on the potential validity of all study data and was to be avoided wherever possible.

If patients were not willing to come back to study visits, the sites were encouraged to investigate patient barriers to study visit compliance and discuss with the study monitor if there was any alternative follow-up schedule that would meet patient expectations. Prior to implementing alternative follow-up schedules, AstraZeneca approval was to be granted.

The dose modifications and discontinuation are acceptable.

This was a multi-center study conducted across 16 countries at a total of 53 sites: Africa and Asia; Kenya (5), India (6), Uganda (2), Egypt (6), Lebanon (2), Ghana (2), South Africa (2), Tanzania (1), Europe; UK (4), Turkey (3), Spain (3), Italy (3), Belgium (2), Greece (1),

North and South America; Brazil (4), US (7). The international coordinating Investigator for this study was Dr. Matthew Heeney, Associate Professor of Pediatrics, Harvard Medical School, 300 Longwood Ave, Boston MA 0215, USA. Administrative structure further consisted of study personnel at the study centers, AstraZeneca study personnel, and the DMC. There was no affiliated contract research organization.

Table 19 Schedule of Assessments (HESTIA3)

	Screening period	Treatment period[a]										Follow-up period	For details see CSP Section
	Enrol-ment	Random-isation											
Visit Number	1	2	3	4	6	9	12	15	18	21	24	End of Study (EOS)	Safety Follow-up	
Day/Week/Month	-7 d	0 d	2 wk	4 wk	3 mo[b]	6 mo[b]	9 mo[b]	12 mo[b]	15 mo[b]	18 mo[b]	21 mo[b]	{12 to 24 mo}	14 d after EOS	
Visit Window	-28 to -7 d	N/A	±3 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±14 d	±5 d	
Signed and dated informed consent/assent	X													10.4
Inclusion/exclusion criteria	X	X[a]												3.1 and 3.2
Assign E-code via IxRS	X													3.3
Relevant SCD, medical and surgical history	X													4.1
SCD diagnosis (if needed)	X													4.1
Demographics[c]	X													4.1
Transcranial Doppler[d]	X													4.1
Ophthalmology examination (if not performed within previous 12 months)[d]	X													4.1
Randomisation via IxRS		X												3.3 and 3.5
BP and pulse rate	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.4
Weight and height	X	X[e]				X		X		X		X		5.2.4
Physical examination (complete/brief)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.2
12-Lead ECG	X					X						X	X	5.2.3
Malaria testing for symptomatic patients[g]	X													4.1
Virology screen (HIV, HBsAg, and HCV)	X													5.2.1
Blood samples for haematology and clinical chemistry	X	X[h]	X	X		X		X		X		X	X	5.2.1

Source: Applicant submission

	Screening period	Treatment period[a]										Follow-up period	For details see CSP Section
	Enrol-ment	Random-isation											
Visit Number	1	2	3	4	6	9	12	15	18	21	24	End of Study (EOS)	Safety Follow-up	
Day/Week/Month	-7 d	0 d	2 wk	4 wk	3 mo[b]	6 mo[b]	9 mo[b]	12 mo[b]	15 mo[b]	18 mo[b]	21 mo[b]	{12 to 24 mo}	14 d after EOS	
Visit Window	-28 to -7 d	N/A	±3 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±14 d	±5 d	
Blood samples for coagulation (INR, PT and APTT)	X													5.2.1
Urine pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Urine for urinalysis (dipstick)	X	X[h]		X		X		X		X		X	X	5.2.1
Training and handout/collection of eDevice		X										X		
Review of eDevice device entries and reminder of use[j]			X	X	X	X	X	X	X	X	X	X		5.3.1
HRQL (PedsQL) assessment[k]		X				X		X		X		X		5.1.3
Palatability/swallowability[l]		X				X								5.3.1
Blood sampling for pharmacokinetics[m]		X		X		X		X		X		X		5.4
Blood sampling for pharmacodynamics (VASP)[m]		X		X		X		X		X		X		5.5
Dispense IP		X			X	X	X	X	X	X	X			7
Return IP and IP accountability			X	X	X	X	X	X	X	X	X	X		7.5 and 7.6
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Adverse event collection (AEs and SAEs)	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	6

[a] Confirmation that patient still met inclusion and exclusion criteria prior to randomising the patient in IxRS; SCD diagnostic testing not necessary if documented in medical records.

[b] Interval must not have been more than 100 days to ensure tablet supply for all days.

[c] Age was required, but partial birthdate (year/month) was allowed if full data were not allowed or known.

[d] See inclusion criteria number 4 for TCD and number 5 for ophthalmology exam. Results must have been available prior to randomisation and these examinations should thereafter have been done annually during the study period.

[e] Only weight was to be measured at Visit 2.

[f] A complete physical examination was to be performed at Visit 1, EOS and Follow-up Visit and a brief examination at all other visits (see CSP Section 5.2.2).

[g] Local/standard tests were to be used for diagnosis of malaria for patients who were symptomatic at Screening.

[h] If the patient had had any serious illness after Visit 1 but before Visit 2, the need for repeated eligibility laboratory sampling must have been evaluated before randomisation. If the Visit 1 laboratory results were less than 10 days old at randomisation, they could replace randomisation safety laboratory sampling to minimise the blood volume drawn.

[i] For females of childbearing potential.

[j] Electronic recording of worst pain according to FPS-R/FLACC and localisation of pain after experiencing a VOC, analgesic use and absence from school/work due to SCD.

[k] The HRQL (PedsQL) instruments were patient-reported if 5-7 years, 8-12 years, or 13-18 years and reported by a caregiver if the patient was ≤4 years.

[l] Morning dose of IP was to be taken at the site. The palatability/swallowability questionnaire assessed by an observer in children ≤4 years, and by Facial Hedonic Scale (FHS) for children ≥ 5 years.

[m] Samples for PK and PD analysis were to be taken 0 hour (pre-dose) and 2 hours post-dose at specified visits and in case of changed dose due to weight increase. No pre-dose PK sample at Visit 2.

[n] SAEs were to be collected from when the ICF was signed. AEs were to be collected from time of randomisation.

Note: In case of modified follow-up when IP is discontinued, the study site visits could be replaced with telephone contact visits as per Table 4.

AE, Adverse event; APTT, Activated partial thromboplastin time; BP, Blood pressure; CSP, clinical study protocol; d, Day; ECG, Electrocardiogram; eDevice Electronic device; EOS, End of study; FLACC, Face, Legs, Activity, Cry, Consolability Scale; FPS-R, Faces Pain Scale - Revised; HBsAg, Hepatitis B surface antigen; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HRQL Health-related quality of life; ICF, Informed consent form; INR, International normalised ratio; IP, Investigational product; IxRS, Interactive Voice/Web Response System; mo, Month; PD, Pharmacodynamics; PedsQL, Paediatric Quality of Life Inventory; PK, Pharmacokinetics; PT, Prothrombin time; SAE, Serious adverse event; SCD, Sickle cell disease; TCD, Transcranial Doppler; VASP, Vasodilator-stimulated phosphoprotein; VOC, Vaso-occlusive crisis; wk, Week.

Source: Applicant submission

Table 20 Schedule of Assessments - Telephone Visits During Treatment Period (HESTIA3)

	Treatment period [a]								For details see Protocol Section
Visit Number	**5**	**7, 8**	**10, 11**	**13, 14**	**16, 17**	**19, 20**	**22, 23**	**25, 26**	
Month	**2**	**4, 5**	**7, 8**	**10, 11**	**13, 14**	**16, 17**	**19, 20**	**22, 23**	
Visit Window	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	
Reminder of eDevice use and ensure data collection of potential VOC events [b]	X	X	X	X	X	X	X	X	5.1.1
Concomitant medications	X	X	X	X	X	X	X	X	7.7
Adverse event collection (AEs and SAEs)	X	X	X	X	X	X	X	X	6

[a] See CSP Appendix E, a Guide for Scheduled Telephone Visits.

[b] Electronic recording of pain according to FPS-R/FLACC when experiencing a VOC, analgesic use and absence from school/work due to SCD.

AE, Adverse event; CSP, Clinical study protocol; d, Day; eDevice, Electronic device; FLACC, Face, Legs, Activity, Cry, Consolability Scale; FPS-R, Faces Pain Scale - Revised; SAE, Serious adverse event; SCD, Sickle cell disease; VOC, Vaso-occlusive crisis.

Source: Applicant submission

Dietary Instructions: Intake of grapefruit juice is not allowed.

Concomitant medications restricted during the study were as follows:

1. Platelet aggregation inhibitors: NOT ALLOWED
   - Other adenosine diphosphate (ADP) receptor blockers - cangrelor, clopidogrel, prasugrel, ticlopidine
   - Dipyridamole
   - Cilostazol
   - Aspirin

2. Anticoagulants: NOT ALLOWED
   - Coumarins – warfarin
   - Heparins (except for flushing venous catheters prior to sampling)
   - Factor Xa inhibitors - fondaparinux, apixaban, rivaroxaban, edoxaban
   - Thrombin inhibitors - bivalirudin, dabigatran, argatroban, desirudin, lepirudin.

3. Non-steroidal anti-inflammatory agents: NOT ALLOWED if chronically used, requiring treatment >3 days/week.

   - Propionic acid derivates - ibuprofen, dexibuprofen, naproxen, ketoprofen
   - Acetic acid derivates - indomethacin, ketorolac, tolmetin, sulindac, diclofenac
   - Enolic acid derivates - piroxicam, meloxicam, tenoxicam
   - Selective COX-2 inhibitors - celecoxib, parecoxib, etoricoxib
   - Others - clonixin.

4. CYP3A inhibitors: NOT ALLOWED as they substantially increase ticagrelor exposure.
   - Strong inhibitors - boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
   - Intake of grapefruit juice.

5. CYP3A substrates or inducers: NOT ALLOWED as they reduce ticagrelor exposure and may result in reduced efficacy.
   - Rifampin/rifampicin
   - Rifabutin
   - Rifapentine
   - Phenytoin
   - Carbamazepine
   - Phenobarbital
   - Avasimibe
   - St. John's wort
   - Simvastatin/lovastatin (metabolized by CYP3A- increases their concentration - avoid doses greater than 40 mg)

6. P-glycoprotein interactions
   - Digoxin - If the patient is receiving digoxin, levels should be monitored closely following initiation of investigational product (IP) and with any change in IP.
   - Cyclosporine - NOT ALLOWED as it increases ticagrelor exposure.

The administration of IP (ticagrelor or placebo) was recorded in the appropriate sections of the eCRF.

Each time IP was dispensed, compliance was reinforced. The caregiver was asked to bring all unused IP and empty bottles to the study site at each on-site visit. When IP was returned, compliance was assessed based upon an interview with the caregiver and a count of the tablets returned.

There were no rescue medications planned in the trial.

The study could be terminated at individual centers per agreement between the Principal Investigator (PI) and AstraZeneca, eg, if the study procedures were not being performed according to GCP, or if recruitment was slow. Enrollment in a country could be terminated in order to ensure a reasonable international distribution of patients.

AstraZeneca could also terminate the entire study prematurely if concerns for safety arose within this study or in any other study with ticagrelor.

Patients were free to withdraw from the study at any time (ie, permanently discontinue IP and study schedule assessments), without prejudice to further treatment.
Withdrawal of consent from the study was to be documented by the Investigator in the patient medical records and recorded in the eCRF as well as in the ICF. The reason for permanent discontinuation of IP, the date of the last dose of the IP, reason for withdrawal and the presence of any AEs had to be documented in the eCRF. The Investigator followed up AEs outside of the clinical study. The patient was to return the eDevice.

If a patient withdrew from participation in the study, then his/her enrolment/randomization code could not be reused. Withdrawn patients were not replaced after randomization.

On 15 June 2020, AstraZeneca received a recommendation from the DMC to terminate the HESTIA3 study, on the grounds that *'the risks to patients of continuing the study outweigh any possibility that ticagrelor may show a beneficial effect if the study were completed'*. The study was fully recruited at the time of the DMC recommendation, with 193 patients randomized at 53 sites across 16 countries in Africa and Asia, Europe and North and South America.

As a result of the premature study termination, the end of study visit was defined by a CSED corresponding to the date of communication to all Investigators to immediately discontinue study treatment administration for all patients who were still on study treatment. This occurred on 18 June 2020. All participating patients had their IP stopped by 23 June 2020, and the last visit of the last patient was on 13 August 2020. The database was locked on 23 September 2020.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up was to be recorded in the eCRF.

As a result of the premature termination, the end of study visit was defined by a common study end date (18 June 2020) corresponding to the date of communication to all Investigators to immediately discontinue study treatment administration for all patients who were still on study treatment. All participating patients had their IP stopped by 23 June 2020, and the last visit of the last patient was on 13 August 2020.

A small proportion of patients withdrew consent or were lost to follow-up: 2 patients (2%) in the ticagrelor group and 5 (5.4%) in the placebo group withdrew their consent. One patient (1%) in the ticagrelor group was randomized in error, consent was not withdrawn for this patient, who did not attend any visits after randomization and who was confirmed alive at the

end of the study. One patient (1%) in the ticagrelor group was lost to follow-up.

Study Endpoints

The primary Endpoint of the trial was the number of VOC's.
Due to the ticagrelor mechanism of action and the potential to reduce symptoms caused by ischemia during a vasoocclusion, a composite endpoint with painful crises and/or ACS was selected for the primary endpoint. Painful crisis is the most common reason for emergency department visits for patients with SCD with a significant impact on young patients' lives, affecting them physically and emotionally. Acute chest syndrome is a potentially life-threatening condition involving vasoocclusion, eg, when caused by pulmonary infarction or indirectly because of fat embolism secondary to bone marrow infarction, and/or a pulmonary infection (Vichinsky EP, 2000). Both painful crises and/or ACS are identified by patients/parents as the acute SCD-related complications having the most impact on their lives (FDA, 2014), and these endpoints are commonly used for evaluation of clinical outcome in trials in SCD.

As listed in table x in section 3, at the End of Phase II Meeting on June 27, 2017, the sponsor and FDA agreed on the proposed design of HESTIA3. On January 10, 2018, at the Type C Meeting, the sponsor and FDA agreed on the endpoints and clinical outcome assessment strategy for HESTIA3.

A VOC occurring during the study should be recorded by the Investigator both as a primary endpoint event, and also as an AE. A potential VOC judged by the Investigator not to fulfil the definition of the primary endpoint should be also recorded as an AE according to standard AE reporting procedures.

Patients were supplied with a handheld eDevice for the treatment period. Caregivers must be willing to learn and use the eDevice and/or supervise the use of the eDevice. At Visit 2, all patients and their caregiver were carefully instructed and trained on how to handle and complete the eDevice.

Collection of some information related to the potential VOC was to be done by the patient/caregiver in real-time in the eDevice, and not based on recollection at the next planned visit. When information related to a potential VOC was entered in the eDevice, the Investigator was to be alerted and should, unless a contact already occurred, call the caregiver within 72 hours from the onset of the potential event to enable a medical consultation and event data Collection. Families were instructed to call the site in case of a VOC, unless already contacted by the site within 72 hours.

Following information was captured in the eDevice to be reviewed by the Investigator:

- Start and stop date/time of the VOC event
- Assessment of worst pain intensity will be done once daily throughout the duration the VOC event (Patient/Observer Reported)
- Report of anatomical location(s) of pain will be done once daily throughout the duration of the VOC event (Patient/Observer Reported).
- If analgesics are taken during the VOC (Yes/No) and the Investigator will enter details of the analgesics (ie, name, type, dose, routes of administration, frequency) into the eCRF.

The following data was collected in the eCRF, based on review of eDevice entries, information from the medical consultation and copies from other medical facilities:

- Confirmation if the event fulfils the VOC definition
- Date of any telephone contact
- Start and stop date/time of the event
- Primary setting for VOC treatment (eg, in-patient hospitalization, short-stay outpatient unit, emergency department or self-treated)
- Start and stop date/time of any in-patient hospitalization
- Treatments administered of the event
- Complete AE/SAE form.

The data collection instrument was appropriate for the trial.

However, with the primary endpoint of the study based on patient (vs clinician/ personnel) input into an "eDevice," there is room for error in that pain (of a VOC) is a subjective measure and may be rated differently by different patients. Where some patients eager to report may input a mild pain episode or VOC, others not as eager or not considering a mild VOC "strong enough," may not report into their device. The endpoint is also dependent on knowledge of use of the eDevice, as well as on the device working well; where in some of the under-developed countries in this study, patients may not be as technologically savvy, affecting their in-putting of VOC episodes into their device. Further, patients in these under-developed countries may not have easy access or reliable transportation to clinicians and medical facilities if VOC pain were to become strong enough to need intravenous pain control, compared to patients in more developed countries.

The secondary endpoints incorporated into the statistical plan of the study were all appropriate. The secondary endpoints included the number of painful crises, the number of ACSs, the duration of the painful crises, the number of VOC's requiring hospitalization or emergency department visits, the number of acute SCD complications, the number of days hospitalized for acute SCD complications, the number of SCD related RBC transfusions, the HRQL total score and by dimension using PedsQL SCD Module and Fatigue total score and by

dimension using the Peds QL Multidimensional Fatigue Scale in order to describe HRQL and fatigue, the proportion of days of absence from school or work, the intensity of worst pain daily during VOC, type of analgesic use, and an assessment of palatability and swallowability of the drug. The safety endpoints were the number of AEs/ SAEs, including bleeding episodes, as well as vital signs, and laboratory safety variables.

Statistical Analysis Plan

As listed in Table 4, at the End of Phase II Meeting on June 27, 2017, the sponsor and FDA agreed on the proposed design of HESTIA3. On January 10, 2018, at the Type C Meeting, the sponsor and FDA agreed on the clinical outcome assessment strategy, including the statistical plan before it was finalized and the results were known.

The primary analysis was based on the intent-to-treat (ITT) principle. The number of VOCs will be analyzed using negative binomial regression. The response variable is the number of VOCs experienced by a patient over the treatment period. Patient follow-up time (log-transformed) will be included as an offset in the linear predictor to adjust for patients having different exposure times. Additional covariates to be adjusted for in the linear predictor will be treatment group (placebo as reference group) and hydroxyurea therapy (Yes/No). The treatment effect will be tested at a 5% significance level. If the negative binomial distribution is not appropriate, a Wilcoxon rank sum test will be used. Ticagrelor data will be pooled and analyzed irrespective of dose.

Ticagrelor data were pooled and analyzed irrespective of dose. The treatment period started at randomization (Visit 2) and continued to EOS Visit regardless of whether the patient prematurely discontinued study treatment. Due to a premature termination of the study by the Sponsor, AstraZeneca, the EOS Visit was defined by a CSED corresponding to the date of communication to all Investigators to immediately discontinue study treatment administration for all patients still on study treatment (18 June 2020). The number of VOCs was analyzed using negative binomial regression. Any VOC event with an onset date within 7 days from a prior event onset date was not counted as a new event. The response variable was the number of VOCs experienced by a patient over the treatment period. Patient follow-up time in years (log-transformed) was included as an offset in the linear predictor to adjust for patients having different follow-up times. Additional covariates adjusted for in the linear predictor were treatment group (placebo as reference group) and baseline hydroxyurea therapy (Yes/No). The treatment effect was tested at a 5% two-sided significance level.

If the negative binomial distribution was not appropriate, a Wilcoxon rank sum test was used. As the Wilcoxon rank sum test cannot be adjusted for the patients' follow-up time, sensitivity analyses were performed to ensure robustness of the results.

The primary analysis includes all data until patients withdraw from the study regardless of if they discontinue from randomized treatment. The primary analysis uses the negative binomial regression model with logarithm of the observation period as an offset term and assumes that missing data is missing at random. Hence, the model assumes that the frequency-of-events during an unobserved period is the same as the frequency estimated using observed data.

To examine the sensitivity of the results and the robustness of this assumption analyses will be performed using controlled multiple imputation method. For this method, an underlying negative binomial stochastic process for the number of VOCs is assumed and post study withdrawal counts will be imputed based on the observed number of events prior to the withdrawal.

Missing data analyses included but were not limited to:

- Missing counts in each treatment group are imputed assuming the expected event rate within that treatment group. This method corresponds closely to the original model and the results are expected to correspond closely to the primary analysis. This analysis was included to allow for comparison with the partial-DRMI method.

- Multiple imputation based on dropout reason (partial-DRMI); Missing counts were to be imputed differently depending on the reason for dropout; meaning that counts for patients in the ticagrelor treatment group who withdrew consent for a potential treatment related reason were imputed based on the expected event rate in the placebo group, whereas the remaining patients who had withdrawn consent were imputed assuming missing at random. Potential treatment-related reasons include but are not limited to AEs, deaths and development of study specified reasons.

Protocol Amendments

On April 20,2020 a protocol amendment was approved to provide details to the allowed modifications of study conduct during the COVID 19 pandemic including visits, IP administration, and procedures. Otherwise, no substantial protocol amendments were made.

6.2.2 Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that the study was performed in compliance with Good Clinical Practice, including the archiving of essential documents, obtaining informed consent prior to treatment, and oversight by Independent Ethics Committees.

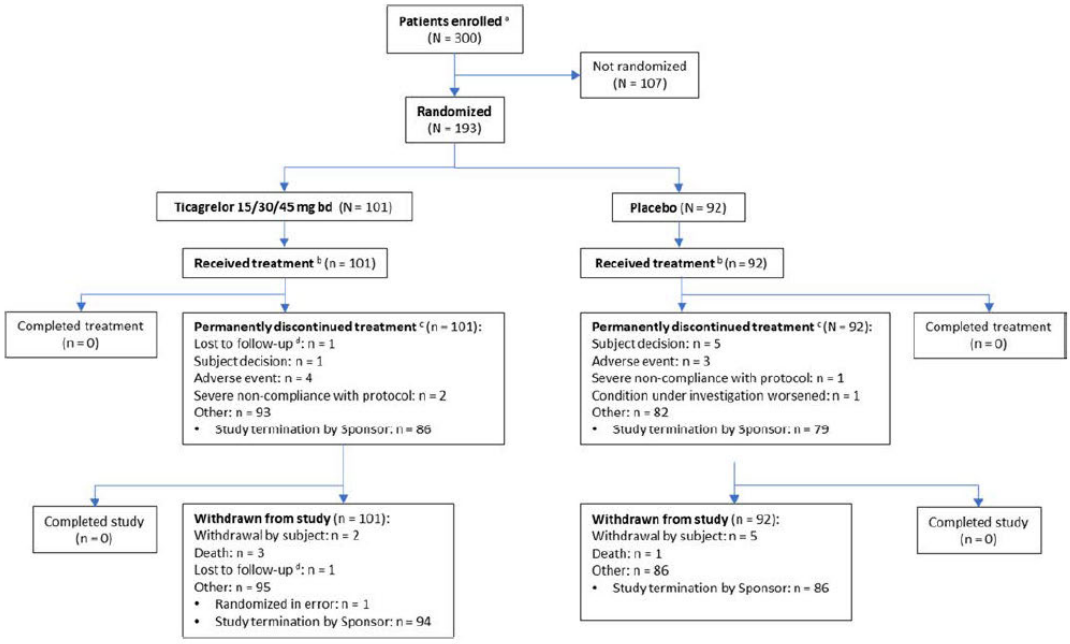
Financial Disclosure

The applicant has adequately disclosed financial interests/ arrangements with clinical investigators as recommended in the guidance for industry. Overall, there are no financial interests or arrangements to disclose by the investigators. (See section 13.2 for further detail). There were 3 investigators with certification of due diligence or lack of disclosure. There is no concern in regard to this affecting the integrity of the data, as acceptable explanations are provided for each investigator (generally the investigators in question at these study sites left the study institution early on in the study and were later unable to be contacted). Further, no concerns are raised given the study design (being double blinded, randomized) minimizes any potential bias, should any of these investigators have had financial affiliations.

There were no notable differences in patient disposition between the treatment groups.

The first patient was enrolled in the study on 26 September 2018 and the last patient was enrolled on 26 September 2019. The last patient was randomized on 18 October 2019. The disposition of the study population is shown in Figure 6 and summarized in Table 21.

Figure 6 Patient Disposition (HESTIA3)



[a] Informed consent/assent received.
[b] Randomised to double-blind study treatment and received at least 1 dose of double-blinded, randomised study treatment.
[c] Includes patients who prematurely discontinued study treatment.
[d] Lost to Follow-up: Patients were only considered lost-to-follow-up after 3 documented failed attempts to reach the patient and all other options of reaching the patient had been exhausted.
bd Twice daily
Source: derived from Table 14.1.1.

Source: Applicant submission

Table 21 Patient Disposition (HESTIA3)

	Number (%) of patients		
	Ticagrelor 15/30/45 mg bd	**Placebo**	**Total**
Patients enrolled [a]			300
Patients randomised	101	92	193
Patients not randomised			107
Failure to meet randomisation criteria			102
Withdrawal by patient			5
Patients who received study treatment [b]	101 (100)	92 (100)	193 (100)
Patients who completed study treatment	0	0	0
Patients who discontinued study treatment [c]	101 (100)	92 (100)	193 (100)
Patient lost to follow-up	1 (1.0)	0	1 (0.5)
Patient decision	1 (1.0)	5 (5.4)	6 (3.1)
Adverse event	4 (4.0)	3 (3.3)	7 (3.6)
Severe non-compliance with protocol	2 (2.0)	1 (1.1)	3 (1.6)
Condition under investigation worsened	0	1 (1.1)	1 (0.5)
Development of study-specific discontinuation criteria	0	0	0
Other	93 (92.1)	82 (89.1)	175 (90.7)
Due to Covid-19 pandemic [d]	4 (4.0)	4 (4.3)	8 (4.1)
Patients who completed study	0	0	0
Patients withdrawn from study	101 (100)	92 (100)	193 (100)
Withdrawal by patient	2 (2.0)	5 (5.4)	7 (3.6)
Death	3 (3.0)	1 (1.1)	4 (2.1)
Lost to follow-up	1 (1.0)	0	1 (0.5)
Other	95 (94.1)	86 (93.5)	181 (93.8)
Randomised in error	1 (1.0)	0	1 (0.5)
Study termination by Sponsor	94 (93.1)	86 (93.5)	180 (93.3)
Due to Covid-19 pandemic	0	0	0

Source: Applicant submission

[a] Informed consent/assent received.
[b] Randomised to double-blind study treatment and received at least 1 dose of double-blinded, randomised study treatment.
[c] Includes patients who prematurely discontinued study treatment.
[d] Patients who discontinued IP due to COVID-19 are also reported in one of the other reasons listed. Due to a data synchronisation error, 1 patient in the ticagrelor group and 3 patients in the placebo group are reported to have permanently discontinued IP due to COVID-19, instead of temporarily discontinuing IP due to COVID-19.

Percentage based on the total number of patients randomised, overall and by treatment group.
bd, twice daily; Covid-19, Coronavirus disease 2019.
Source: derived from Table 14.1.1.

Source: Applicant submission

Protocol Violations/Deviations

In general, there were no concerns regarding important protocol deviations in terms of the quality of study conduct, ability to analyze the primary efficacy data, or with respect to the safety profile observed within the patient population described.

The number of patients with important protocol deviations in each treatment group is summarized in Table 22

Overall, 102 (52.8%) of the randomized patients had at least 1 important protocol deviation: 54 patients on ticagrelor and 48 on placebo. Deviations related to efficacy and study procedures were the most common. The efficacy criteria deviations (ticagrelor 27 patients [26.7%]; placebo 15 patients [16.3%]) were mainly related to missing or incorrect questionnaires completed captured as part of the secondary endpoints. Overall, 14 patients (7.3%) had protocol deviations related to concomitant medications. These were balanced between the 2 treatment groups.

Thirty-two patients (16.6%) overall had IP administration criteria deviations. These included patients with study treatment compliance of < 80% or > 120%. A small number of patients overall (9 patients [4.7%]) had important protocol deviations related to eligibility and entry criteria.

Thirty patients (29.7%) in the ticagrelor group and 20 (21.7%) in the placebo group had important protocol deviations related to study procedures. These mainly pertain to the availability of the PK/PD data.

There were no COVID-related important protocol deviations identified.

Reviewer Comment: The protocol violations were not substantial enough to impact the results

of the trial.

Table 22 Protocol Deviations (HESTIA3)

Important protocol deviation [a]	Number (%) of patients		
	Ticagrelor 15/30/45 mg bd (N = 101)	Placebo (N = 92)	Total (N = 193)
Patients with at least one important protocol deviation	54 (53.5)	48 (52.2)	102 (52.8)
Concomitant medication criteria	7 (6.9)	7 (7.6)	14 (7.3)
Efficacy criteria	27 (26.7)	15 (16.3)	42 (21.8)
Eligibility and entry criteria	4 (4.0)	5 (5.4)	9 (4.7)
IP administration criteria	15 (14.9)	17 (18.5)	32 (16.6)
Study procedures criteria	30 (29.7)	20 (21.7)	50 (25.9)
Patients with at least one COVID-19 related important protocol deviation	0	0	0

[a] A patient may have one or more important protocol deviations and is counted once in each category.
Percentage based on the total number of patients in the full analysis set, overall and by treatment group.
bd, twice daily; COVID-19, Coronavirus disease 2019; IP, investigational product; N, total number of patients in treatment group.
Details of each important protocol deviation is described in Listing 16.2.2.1.
Source: Table 14.1.2.

Source: Applicant submission

Table of Demographic Characteristics

The demographic characteristics of the study population are summarized in Table 23 and Table 24. At baseline, the mean age of the patients was 10.3 years (range 3 to 17 years); 115 patients (59.6%) were in the age group ≥ 2 years to < 12 years, with 78 patients (40.4%) in the age group ≥ 12 to < 18 years; 111 patients (57.5%) were Black or African American, 46 patients (23.8%) were White and 30 patients (15.5%) were Asian; 102 (52.8%) patients were male. Overall, 69 patients (35.8%) were in the weight group ≥ 12 to ≤ 24 kg, 101 (52.3%) were in the weight group > 24 to ≤ 48 kg, and 23 (11.9%) were in the group > 48 kg at baseline. The randomized treatment groups were balanced with respect to demographic characteristic at baseline. The demography was as expected and similar to earlier studies in this population.

Table 23 Demographic Characteristics (HESTIA3)

Demographic characteristic		Number (%) of patients		
		Ticagrelor 15/30/45 mg bd (N = 101)	Placebo (N = 92)	Total (N = 193)
Age (years) [a]	n	101	92	193
	Mean	10.4	10.1	10.3
	SD	4.1	3.8	4.0
	Median	10.0	10.5	10.0
	Min	3.0	3.0	3.0
	Max	17.0	17.0	17.0
Age group (years)	< 12	61 (60.4)	54 (58.7)	115 (59.6)
	≥ 12	40 (39.6)	38 (41.3)	78 (40.4)
	Total	101 (100.0)	92 (100.0)	193 (100.0)
Sex, n (%)	Male	53 (52.5)	49 (53.3)	102 (52.8)
	Female	48 (47.5)	43 (46.7)	91 (47.2)
	Total	101 (100.0)	92 (100.0)	193 (100.0)
Race, n (%)	White	25 (24.8)	21 (22.8)	46 (23.8)
	Black or African American	60 (59.4)	51 (55.4)	111 (57.5)
	Asian	15 (14.9)	15 (16.3)	30 (15.5)
	Native Hawaiian or other Pacific Islander	0	0	0
	American Indian or Alaska Native	0	0	0
	Other	1 (1.0)	5 (5.4)	6 (3.1)
	Total	101 (100.0)	92 (100.0)	193 (100.0)
Ethnicity	Hispanic or Latino	7 (6.9)	5 (5.4)	12 (6.2)
	Not Hispanic or Latino	94 (93.1)	87 (94.6)	181 (93.8)
	Total	101 (100.0)	92 (100.0)	193 (100.0)

Source: Applicant submission

Table 24 Demographic Characteristics (Height, Weight, BMI) (HESTIA3)

Baseline characteristic		Ticagrelor 15/30/45 mg bd (N=101)	Placebo (N=92)	Total (N=193)
Height (cm)	n	101	92	193
	Mean	134.3	132.3	133.4
	SD	21.03	18.88	20.01
	Median	134.0	134.0	134.0
	Min	71	86	71
	Max	180	179	180
Weight (kg)	n	101	92	193
	Mean	31.28	29.80	30.57
	SD	14.396	11.564	13.110
	Median	27.50	27.40	27.50
	Min	12.5	12.0	12.0
	Max	73.6	65.9	73.6
Body mass index (kg/m²)	n	101	92	193
	Mean	16.536	16.368	16.457
	SD	3.7431	2.8847	3.3539
	Median	15.264	15.716	15.556
	Min	9.94	11.95	9.94
	Max	31.74	26.31	31.74
Weight group (kg) n (%)	>=12 to <=24	40 (39.6)	29 (31.5)	69 (35.8)
	>24 to <=48	44 (43.6)	57 (62.0)	101 (52.3)
	>48	17 (16.8)	6 (6.5)	23 (11.9)
	Total	101 (100.0)	92 (100.0)	193 (100.0)

Percentage based on the total number of patients in the full analysis set with non-missing data (i.e. 'Total' row), overall and by treatment group.
Baseline is the last assessment collected (scheduled or unscheduled) prior to the first dose of study treatment, or last assessment collected prior to or at the randomisation (Visit 2), for patients who are randomised but do not receive any treatment.
N Total number of patients in treatment group. n Number of patients included in analysis. Max Maximum. Min Minimum. SD Standard deviation. bd Twice a day.

[Source: ASTRAZENECA\TICAGRELOR\LYA10053\BIOSTATISTICS\PRODUCTION\TABLES\DM201.SAS] (b) (4) 26NOV2020

Source: Applicant submission

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 25 summarizes the number of VOCs experienced within the last 12 months prior to enrolment in the study. Most patients (188 [97.4%]) had experienced between 2 and 4 VOCs in the 12 months before enrolment. Two patients in each treatment group had experience more than 4 VOCs in the past 12 months.

Table 25 Vaso-Occlusive Crises within the 12 Months Prior to Enrollment (HESTIA3)

Disease characteristic		Number (%) of patients		
		Ticagrelor 15/30/45 mg bd (N = 101)	Placebo (N = 92)	Total (N = 193)
Number of prior VOCs, n (%) [a]	≤ 1	0	1 (1.1)	1 (0.5)
	≥ 2 to ≤ 4	99 (98.0)	89 (96.7)	188 (97.4)
	> 4	2 (2.0)	2 (2.2)	4 (2.1)
Primary setting for prior VOC treatment, n (%) [b]	In-patient hospitalisation	51 (50.5)	45 (48.9)	96 (49.7)
	Emergency department	6 (5.9)	9 (9.8)	15 (7.8)
	Short-stay outpatient unit	32 (31.7)	21 (22.8)	53 (27.5)
	Medical clinic outpatient	32 (31.7)	40 (43.5)	72 (37.3)
	Self-treated [c]	11 (10.9)	8 (8.7)	19 (9.8)
	Medically supervised outpatient treatment with escalated pain medication	5 (5.0)	1 (1.1)	6 (3.1)
	Other	0	0	0
Duration from start of last prior VOC to randomisation date [d]	n	101	92	193
	Mean	118.7	106.3	112.8
	SD	82.37	72.43	77.84
	Median	94.0	82.5	86.0
	Min	20	12	12
	Max	367	331	367

[a] Patients with ≤ 1 prior VOC event are protocol deviations.
[b] A patient can have > 1 primary setting reported for VOC treatment and is counted once in each category.
[c] No consultation with medical personnel prior to escalation of pain medication.
[d] Duration (days) = (date of randomisation [Visit 2] – start date of last prior VOC event) + 1

Percentage based on the total number of patients in the full analysis set, overall and by treatment group.
bd, Twice daily; Max, Maximum; Min, Minimum; N, Total number of patients in treatment group; n, Number of patients included in analysis; SD, Standard deviation; VOC, Vaso-occlusive crisis.

Source: Applicant submission

Table 26 summarizes the SCD characteristics at baseline. Most (170 [88.1%]) of the randomized patients (FAS) were confirmed as having the SCD genotype HbSS; 22 (11.4%) had HbS/β^0 thalassemia. For SCD complication, 5 patients (2.6%) had a history of ACS, and 29 patients (15.0%) had a history of dactylitis or hand-foot syndrome. The SCD characteristics at baseline were generally balanced between the 2 randomized treatment groups.

Table 26 SCD Characteristics at Baseline (HESTIA3)

Disease characteristic [a]		Number (%) of patients		
		Ticagrelor 15/30/45 mg bd (N = 101)	Placebo (N = 92)	Total (N = 193)
Sickle cell disease genotype, n (%)	HbSS	87 (86.1)	83 (90.2)	170 (88.1)
	HbS/β^0 thalassaemia	13 (12.9)	9 (9.8)	22 (11.4)
	Missing [b]	1 (1.0)	0	1 (0.5)
Number of years since SCD diagnosis [c]	n	100	92	192
	Mean	5.11	4.58	4.86
	SD	4.975	4.431	4.718
	Median	3.75	4.11	4.09
	Min [d]	0.0	0.0	0.0
	Max	16.4	16.5	16.5
Age at diagnosis (years)	n	100	92	192
	Mean	5.39	5.65	5.52
	SD	5.085	4.834	4.955
	Median	4.00	5.00	4.00
	Min	0.0	0.0	0.0
	Max	17.0	17.0	17.0
SCD history of complications, n (%) [e]	Acute chest syndrome	2 (2.0)	3 (3.3)	5 (2.6)
	Asplenia	0	1 (1.1)	1 (0.5)
	Bone necrosis	2 (2.0)	1 (1.1)	3 (1.6)
	Cholelithiasis	1 (1.0)	0	1 (0.5)
	Dactylitis or hand-foot syndrome	17 (16.8)	12 (13.0)	29 (15.0)
	Iron overload	1 (1.0)	0	1 (0.5)
	Leg ulcer	1 (1.0)	0	1 (0.5)
	Priapism	0	1 (1.1)	1 (0.5)
	Pulmonary hypertension	0	1 (1.1)	1 (0.5)
	Splenic sequestration	1 (1.0)	2 (2.2)	3 (1.6)
	Other	4 (4.0)	2 (2.2)	6 (3.1)

[a] Assessed at screening (Visit 1).
[b] This patient had HbSC.
[c] Number of years since SCD diagnosis calculated relative to randomisation (Visit 2).
[d] Patients whose genotype was confirmed at screening.

[e] SCD history of complications includes occurrence within the past 12 months prior to screening (Visit 1) of one or more of the following but excluding any prior VOCs: dactylis/hand-foot syndrome, acute chest syndrome, hepatic sequestration, splenic sequestration, bone necrosis, joint necrosis, priapism, leg ulcer, nephropathy, systemic hypertension, pulmonary hypertension, cholelithiasis, iron overload, cardiomegaly, cardiac failure, coronary artery disease, asplenia, renal impairment and hepatic impairment..

Percentage based on the total number of patients in the full analysis set, overall and by treatment group.

bd, twice daily; HbSS, homozygous sickle cell anaemia; HbS/β^0, sickle beta-zero-thalassaemia; Max, maximum; Min, minimum; N, total number of patients in treatment group; n, number of patients included in analysis; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

Source: Table 14.1.9.

Source: Applicant submission

Disease-related medical history is summarized by system organ class in Table 27. Of the most frequently reported SOCs, the proportion of patients reporting medical history in the following was higher for ticagrelor than for placebo: Blood and lymphatic system disorders (16.8% ticagrelor vs 7.6% placebo) and infections and infestations (13.9% ticagrelor vs 7.6% placebo).

Table 27 Disease Related Medical History (HESTIA3)

System organ class	Number (%) of patients		
	Ticagrelor 15/30/45 mg bd (N = 101)	Placebo (N = 92)	Total (N = 193)
Blood and lymphatic system disorders	17 (16.8)	7 (7.6)	24 (12.4)
Cardiac disorders	2 (2.0)	3 (3.3)	5 (2.6)
Congenital, familial and genetic disorders	0	2 (2.2)	2 (1.0)
Eye disorders	7 (6.9)	2 (2.2)	9 (4.7)
Gastrointestinal disorders	6 (5.9)	3 (3.3)	9 (4.7)
General disorders and administration site conditions	1 (1.0)	0	1 (0.5)
Hepatobiliary disorders	6 (5.9)	2 (2.2)	8 (4.1)
Immune system disorders	1 (1.0)	1 (1.1)	2 (1.0)
Infections and infestations	14 (13.9)	7 (7.6)	21 (10.9)
Injury, poisoning and procedural complications	1 (1.0)	1 (1.1)	2 (1.0)
Investigations	2 (2.0)	2 (2.2)	4 (2.1)
Metabolism and nutrition disorders	3 (3.0)	4 (4.3)	7 (3.6)
Musculoskeletal and connective tissue disorders	5 (5.0)	7 (7.6)	12 (6.2)
Nervous system disorders	1 (1.0)	1 (1.1)	2 (1.0)
Psychiatric disorders	4 (4.0)	1 (1.1)	5 (2.6)
Renal and urinary disorders	3 (3.0)	2 (2.2)	5 (2.6)
Reproductive system and breast disorders	1 (1.0)	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	10 (9.9)	6 (6.5)	16 (8.3)
Skin and subcutaneous tissue disorders	2 (2.0)	3 (3.3)	5 (2.6)
Social circumstances	1 (1.0)	0	1 (0.5)
Surgical and medical procedures	1 (1.0)	0	1 (0.5)
Vascular disorders	0	2 (2.2)	2 (1.0)

Percentage based on the total number of patients in the full analysis set, overall and by treatment group.
Number (%) of patients sorted alphabetically by SOC.
A patient can have one or more preferred terms reported under a given SOC.
bd, Twice daily; N, Total number of patients in treatment group; SOC, System organ class.
MedDRA version 23.0.
Source: Table 14.1.6.

Source: Applicant submission

Relevant surgical history is summarized in Table 28. In the ticagrelor group, 24 patients (23.8%) had a previous surgical or medical procedure, compared with 8 (8.7%) in the placebo group. The most notable difference between the 2 randomized treatment groups was in the number of patients who had a splenectomy

Table 28 Relevant Surgical History (HESTIA3)

System organ class / Preferred term	Number (%) of patients		
	Ticagrelor 15/30/45 mg bd (N = 101)	Placebo (N = 92)	Total (N = 193)
Surgical and medical procedures	24 (23.8)	8 (8.7)	32 (16.6)
Adenoidectomy	1 (1.0)	0	1 (0.5)
Adenotonsillectomy	2 (2.0)	0	2 (1.0)
Appendicectomy	1 (1.0)	1 (1.1)	2 (1.0)
Biliary stent placement	1 (1.0)	0	1 (0.5)
Cholecystectomy	6 (5.9)	2 (2.2)	8 (4.1)
Inguinal hernia repair	1 (1.0)	0	1 (0.5)
Osteomyelitis drainage	0	1 (1.1)	1 (0.5)
Splenectomy	15 (14.9)	4 (4.3)	19 (9.8)
Surgery	0	1 (1.1)	1 (0.5)
Tonsillectomy	2 (2.0)	0	2 (1.0)
Urethral meatotomy	1 (1.0)	0	1 (0.5)

Percentage based on the total number of patients in the full analysis set, overall and by treatment group.
Number (%) of patients sorted alphabetically by SOC and by PT within SOC.
A patient can have one or more preferred terms reported under a given SOC.
bd, Twice daily; N, Total number of patients in treatment group; PT, Preferred term; SOC, System organ class.
MedDRA version 23.0.
Source: Table 14.1.7.

Source: Applicant submission

Reviewer Comment: There is a discrepancy noted between Table 15 and Table 17. Table 15 (demonstrating baseline sickle cell disease characteristics) indicates 0 patients in the ticagrelor group claim asplenia, while in Table 17 (demonstrating baseline surgical history), indicates 15 patients have undergone a splenectomy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance with study treatment was high, as calculated based on pill count and actual study treatment exposure (excluding missed exposure days due to study treatment interruptions). Table 29 summarizes study treatment compliance. Overall, 162 patients (84.4%) had

compliance within the range ≥ 80% to ≤ 120%: 87 patients (87.0%) in the ticagrelor group and 75 (81.5%) in the placebo group.

For 9.4% of the patients the calculated compliance was missing due to the pill count of tablets returned being missing for at least one of the dispensed kits.

Table 29 Study Treatment Compliance (HESTIA3)

Dose level		Ticagrelor 15/30/45 mg bd (N = 100)	Placebo (N = 92)	Total (N = 192)
Overall dose level (15/30/45 mg bd)	n	92	82	174
	Mean	96.19	95.41	95.82
	SD	7.406	8.869	8.114
	Min	61.8	51.3	51.3
	1st quartile	96.42	93.36	94.85
	Median	98.61	98.94	98.71
	3rd quartile	99.76	100.15	99.86
	Max	104.1	112.2	112.2
Overall dose level (15/30/45 mg bd) n (%)	< 80%	5 (5.0)	7 (7.6)	12 (6.3)
	≥ 80% to ≤ 120%	87 (87.0)	75 (81.5)	162 (84.4)
	> 120%	0	0	0
	Missing	8 (8.0)	10 (10.9)	18 (9.4)
	COVID-19 pandemic-related reason	1 (1.0)	0	1 (0.5)
	Non-COVID-19 pandemic-related reason	7 (7 .0)	10 (10.9)	17 (8.9)
Weight-based dose level disagreement n (%) [a]		2 (2.0)	3 (3.3)	5 (2.6)

[a] Number (%) of patients in the safety analysis set with weight-based dose level disagreement at any time over the course of the treatment period and over all dose levels received. Weight (kg) (scheduled or unscheduled), as available at the start of study treatment administration at a given dose level is assessed in accordance with the protocol weight-based specifications to determine dose-level discrepancies and subsequently categorised as presented.

Compliance (%) = (actual tablets taken/expected tablets taken) * 100. Where: 1 tablet = 15 mg.

Actual tablets taken: By dose level: Difference between total tablets dispensed and total tablets returned, regardless of temporary study treatment administration discontinuation (study treatment interruptions).

By overall dose level: Sum of actual tablets taken over all dose levels received.

If tablets returned amount is missing for any/all kit IDs, both dose level and over all dose levels actual tablets taken is missing, ie, no imputation assumptions of tablets taken applied.

Expected tablets taken: By dose level: Expected tablets to be taken per last available weight (kg) at the time of study treatment administration (planned) as based on actual study treatment exposure (days) excluding missed exposure days due to study treatment interruptions. By overall dose level: Sum of expected tablets taken over all dose levels received.

Percentage based on the total number of patients in the safety analysis set, overall and by treatment group.

Source: Applicant submission

The most common allowed concomitant medications (used by > 20% of patients) are summarized in Table 30 by ATC classification. All but 2 patients in the study (99.0%) received concomitant medications that were permitted by the CSP. Overall, 119 (62.0%) of patients received hydroxyurea (hydroxycarbamide). This was equally distributed between the treatment groups.

Table 30 Most Common Allowed Concomitant Medications (HESTIA3)

ATC classification / Generic term	Number (%) of patients		
	Ticagrelor 15/30/45 mg bd (N = 100)	Placebo (N = 92)	Total (N = 192)
Patients with allowed concomitant medication [a]	98 (98.0)	92 (100.0)	190 (99.0)
Folic acid and derivatives	91 (91.0)	87 (94.6)	178 (92.7)
Anilides	75 (75.0)	66 (71.7)	141 (73.4)
Other antineoplastic agents / Hydroxycarbamide	60 (60.0)	59 (64.1)	119 (62.0)
Propionic acid derivatives	54 (54.0)	45 (48.9)	99 (51.6)
Acetic acid derivatives and related substances	37 (37.0)	31 (33.7)	68 (35.4)
Third-generation cephalosporins	35 (35.0)	28 (30.4)	63 (32.8)
Beta-lactamase sensitive penicillins	32 (32.0)	26 (28.3)	58 (30.2)
Penicillins with extended spectrum	34 (34.0)	22 (23.9)	56 (29.2)
Combinations of penicillins, incl. beta-lactamase inhibitors	30 (30.0)	23 (25.0)	53 (27.6)
Electrolyte solutions	32 (32.0)	20 (21.7)	52 (27.1)
Natural opium alkaloids	30 (30.0)	13 (14.1)	43 (22.4)
Other opioids	24 (24.0)	15 (16.3)	39 (20.3)

[a] Number (%) of patients with allowed concomitant medication, in descending frequency of total column by ATC class.
A patient can have medications reported in one or more ATC classes/generic terms and is counted only once per ATC class/generic term.
Includes medications taken at any time on or after the day of first dose of study treatment up to and including the day of last dose of study treatment.
Propionic acid derivatives: Chronic use (> 3 days/week) was not allowed per protocol.
Percentage based on the total number of patients in the safety analysis set, overall and by treatment group.
ATC, Anatomic Therapeutic Chemical (class); bd, Twice daily; N, Total number of patients in treatment group.
WHODrug Global B3-format March 2020.
Source: derived from Table 14.1.11.

Source: Applicant submission

Disallowed concomitant medications are summarized in Table 31. Eight patients in each treatment group (8.3% overall) received disallowed concomitant medication.

Table 31 Disallowed Concomitant Medications (HESTIA3)

ATC classification / Generic term	Number (%) of patients		
	Ticagrelor 15/30/45 mg bd (N = 100)	Placebo (N = 92)	Total (N = 192)
Patients with disallowed concomitant medication [a]	8 (8.0)	8 (8.7)	16 (8.3)
Macrolides	5 (5.0)	5 (5.4)	10 (5.2)
Clarithromycin	5 (5.0)	4 (4.3)	9 (4.7)
Erythromycin	0	1 (1.1)	1 (0.5)
Other analgesics and antipyretics	0	3 (3.3)	3 (1.6)
Carbamazepine	0	3 (3.3)	3 (1.6)
Antihypertensives for pulmonary arterial hypertension	1 (1.0)	0	1 (0.5)
Bosentan	1 (1.0)	0	1 (0.5)
Heparin group	1 (1.0)	0	1 (0.5)
Enoxaparin	1 (1.0)	0	1 (0.5)
Enoxaparin sodium	1 (1.0)	0	1 (0.5)
Propionic acid derivatives [b]	1 (1.0)	0	1 (0.5)
Ketoprofen	1 (1.0)	0	1 (0.5)

[a] Number (%) of patients with disallowed concomitant medication, sorted in descending frequency of total column by ATC class and generic term.

[b] Propionic acid derivatives: Chronic use (> 3 days/week) was not allowed per protocol.

A patient can have medications reported in one or more ATC classes/generic terms and is counted only once per ATC class/generic term.

Includes medications taken at any time on or after the day of first dose of study treatment up to and including the day of last dose of study treatment.

Percentage based on the total number of patients in the safety analysis set, overall and by treatment group.

ATC, Anatomic Therapeutic Chemical (class); bd, Twice daily; N, Total number of patients in treatment group.

WHODrug Global B3-format March 2020.

Source: Table 14.1.10.

Source: Applicant submission

No rescue medications were allowed in the trial since patients were permitted to continue their baseline SCD treatment (hydroxyurea).

Efficacy Results – Primary Endpoint

The primary objective of the study was not met. The analysis demonstrated that ticagrelor was not superior to placebo in reducing the rate of VOCs (composite endpoint of painful crises and/or ACS): the incidence rate ratio was 1.06 (95% CI: 0.75, 1.50), p = 0.7597. (See Table X).

Table 32 Analysis of Primary Efficacy Variable (Number of VOCs); Negative Binomial Model (HESTIA3)

Treatment group	n	Number (%) of patients with events	Total number of VOCs	Total follow-up time (years)	Results		Comparison between treatment groups [a]		
					Estimate: incidence rate (per year) of VOCs (SE)	95% CI	Incidence rate ratio	95% CI	p-value
Ticagrelor 15/30/45 mg bd (N = 101)	101	70 (69.3)	249	89.0	2.74 (0.334)	2.16, 3.48	1.06	0.75, 1.50	0.7597
Placebo (N = 92)	92	58 (63.0)	202	80.0	2.60 (0.336)	2.01, 3.34			

[a] Comparison with placebo.

Model: Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and hydroxyurea use at randomisation included in the model as covariates.

Logarithm of each patient's corresponding follow-up time is used as an offset variable in the model to adjust for patients having different follow-up times during which the events occur.

Goodness of fit: Pearson Chi-square: 173.91 p-value: 0.7925.

Dispersion parameter, negative binomial model: 1.0713

Number of VOCs defined as the count of VOC events assessed throughout the treatment period from randomisation (Visit 2) to End of Study visit or date of premature study discontinuation.

VOC events with an onset date ≤ 7 days of the previous event onset date are not counted as new events.

Percentage based on total number of patients in the full analysis set, by treatment group.

bd, Twice daily; CI, Confidence interval; N, Total number of patients in treatment group; n, Number of patients included in analysis; SE, Standard error; VOC, Vaso-occlusive crisis.

Source: Table 14.2.1.1.2.

Source: Applicant submission

Table 33 presents the summary statistics for the number of VOCs. The mean number of VOCs was 2.5 in the ticagrelor group and 2.2 in the placebo group.

Table 33 Summary Statistics of Number of VOCs (HESTIA3)

Number of VOCs [a]	Ticagrelor 15/30/45 mg bd (N = 101)	Placebo (N = 92)
n	101	92
Mean	2.5	2.2
Standard deviation	3.02	2.63
Median	2.0	1.0
Minimum	0	0
Maximum	17	11

[a] Number of VOCs is defined as the count of VOC events assessed throughout the treatment period from randomisation (Visit 2) to End of Study visit or date of premature study discontinuation.

VOC events with an onset date ≤ 7 days of the previous event onset date are not counted as new events.

bd, Twice daily; N, Total number of patients in treatment group; n, Number of patients included in analysis; VOC, Vaso-occlusive crisis.

Source: Table 14.2.1.1.1.

Source: Applicant submission

The applicant and the FDA are in agreement in regard to the primary efficacy variable analysis.

Reviewer Comment: Additional exploratory analyses were not conducted due to failure of primary endpoint.

Data Quality and Integrity

OSI was not consulted due to the primary endpoint not being met and no indication being sought.

The primary endpoint for the study was not met. The study demonstrated no evidence of benefit for ticagrelor over placebo. The results of the primary efficacy analysis were consistent across the pre-defined subgroups. While the study demonstrates an unfavorable benefit-risk profile for ticagrelor in children aged 2 year to <18 years with SCD, it is worth noting that a greater proportion of the baseline ticagrelor population claimed a relevant medical history involving blood and lymphatic system disorders, infections, and medical procedures (including splenectomy) compare to the placebo population.

The early termination of the study was only 4 months ahead of the anticipated completion date and did not affect the ability to perform the pre-defined analyses. The planned enrolment had completed, with 193 randomized patients, the recruited population was consistent with the intended study population, and the planned age distribution was achieved. The sample size assumption of a mean of 2.0 crises per year on placebo was exceeded.

VASP: Complicated sample preparation procedures and potentially incorrect preparation of samples might have increased the variability of the results. In addition, the number of missing samples resulted in a less robust assessment of the PD in pediatric SCD patients.

eDevice: There are missing data on Pain Assessment for 32.9% of patients with VOCs on ticagrelor and 22.4% on placebo, which has an impact on pain assessment captured on the eDevice. In addition, poor compliance with weekly diaries resulted in missing absence from school/work assessment. The proportion of missing assessments was balanced across the two treatment groups.

Efficacy Results – Secondary and other relevant endpoints

Analyses of secondary efficacy endpoints are summarized in Table 34. Efficacy is not demonstrated in secondary endpoints once the primary endpoint failed. The secondary endpoint results were consistent with the primary endpoint results.

Table 34 Secondary Endpoint Analyses (HESTIA3)

Efficacy variable	Treatment group	n	Number (%) of patients with events	Total number of events	Total follow-up time (years)	Results		Comparison between treatment groups [a]		
						Estimate: Incidence rate (per year) of events (SE)	95% CI	Incidence rate ratio	95% CI	p-value
Number of painful crises [b,c]	Ticagrelor 15/30/45 mg bd	101	69 (68.3)	248	89.0	2.73 (0.339)	(2.14,3.48)	1.02	(0.72,1.45)	0.9037
	Placebo	92	58 (63.0)	209	80.0	2.67 (0.349)	(2.07,3.45)			
Number of individual painful crises [b,d]	Ticagrelor 15/30/45 mg bd	101	69 (68.3)	266	89.0	2.92 (0.371)	(2.28,3.74)	1.03	(0.72,1.48)	0.8573
	Placebo	92	58 (63.0)	221	80.0	2.82 (0.378)	(2.17,3.67)			
Number of ACS events [b,d]	Ticagrelor 15/30/45 mg bd	101	5 (5.0)	6	89.0	0.05 (0.028)	(0.01,0.15)	0.76	(0.17,3.30)	0.7136
	Placebo	92	4 (4.3)	6	80.0	0.06 (0.036)	(0.02,0.19)	0.76	(0.17,3.30)	0.7136
Number of individual ACS events [b,d]	Ticagrelor 15/30/45 mg bd	101	5 (5.0)	6	89.0	0.05 (0.028)	(0.01,0.15)			
	Placebo	92	4 (4.3)	6	80.0	0.06 (0.036)	(0.02,0.19)	0.84	(0.50,1.40)	0.4970
Duration of painful crises (days) *	Ticagrelor 15/30/45 mg bd	101	69 (68.3)	1476	89.0	16.09 (2.864)	(11.35,22.80)			
	Placebo	92	58 (63.0)	1441	80.0	19.20 (3.572)	(13.33,27.64)	1.43	(0.87,2.36)	0.1636
Number of VOCs requiring hospitalisation or emergency department visits [b,c]	Ticagrelor 15/30/45 mg bd	101	42 (41.6)	87	89.0	0.87 (0.147)	(0.62,1.21)			
	Placebo	92	27 (29.3)	51	80.0	0.61 (0.118)	(0.41,0.89)			
Number of days hospitalised for VOCs *	Ticagrelor 15/30/45 mg bd	101	39 (38.6)	526	89.0	5.07 (1.423)	(2.93,8.79)	1.68	(0.76,3.75)	0.2011
	Placebo	92	23 (25.0)	256	80.0	3.01 (0.892)	(1.69,5.38)			
	Ticagrelor 15/30/45 mg bd	101	3 (3.0)	6	89.0	Did not converge		Did not converge		

Efficacy variable	Treatment group	n	Number (%) of patients with events	Total number of events	Total follow-up time (years)	Results		Comparison between treatment groups [a]		
						Estimate: Incidence rate (per year) of events (SE)	95% CI	Incidence rate ratio	95% CI	p-value
Number of acute SCD complications [b]	Placebo	92	2 (2.2)	3	80.0					
Number of days hospitalised for acute SCD complications [e]	Ticagrelor 15/30/45 mg bd	101	0	0	89.0	0.00 (0.000)	(0.00, NC)	0.00	(0.00, NC)	0.9940
	Placebo	92	3 (3.3)	6	80.0	0.00 (0.211)	(0.00, NC)			
Number of sickle cell-related red blood cell transfusions [b f]	Ticagrelor 15/30/45 mg bd	101	21 (20.8)	39	89.0	0.41 (0.106)	(0.25, 0.68)	0.77	(0.38, 1.58)	0.4822
	Placebo	92	19 (20.7)	49	80.0	0.53 (0.136)	(0.32, 0.88)			

[a] Comparison with placebo

[b] Number of secondary endpoint events as assessed throughout the treatment period from randomisation (Visit 2) to EOS visit or date of premature study discontinuation (observed follow-up).

[c] Events with an onset date ≤ 7 days of the previous event onset date are not counted as new events.

[d] Individual painful crisis and ACS events with an onset date ≤ 7 days of the previous event onset date are counted as new events.

[e] For patients not experiencing a secondary endpoint event in the defined treatment period, duration of defined event is set to 0 days.

[f] Sickle cell-related red blood cell transfusions as identified by study physician review.

Model: Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates. Logarithm of each patient's corresponding follow-up time is used as an offset variable in the model to adjust for patients having different follow-up times during which the events occur.

Percentage based on the total number of patients in the full analysis set, by treatment group.

ACS, Acute chest syndrome; bd Twice daily; EOS, End of study; n, Number of patients included in analysis; NC, not calculable; SE, Standard error; SCD, Sickle cell disease; VOC, Vaso-occlusive crisis.

Source: Table 14.2.1.2.2.

Source: Applicant submission

The use of analgesics during VOCs is summarized in Table 35. All patients who had at least one VOC took an analgesic. Most patients (more than 98%) in each treatment group who had VOCs received non-opioid analgesics. Opioid analgesics were taken by 46 patients in the ticagrelor group and by 22 patients in the placebo group. This is supportive of the rate of VOCs being higher in the ticagrelor arm.

Table 35 Use of Analgesics during VOCs (HESTIA3)

	Ticagrelor 15/30/45 mg bd		Placebo	
	Number (%) of patients [a] (N = 101)	Events [b]	Number (%) of patients [a] (N = 92)	Events [b]
Individual VOCs [c]	70 (69.3)	272	58 (63.0)	227
Any analgesics	70 (100.0)	270	58 (100.0)	224
Opioids				
Yes	46 (65.7)	98	22 (37.9)	47
No	57 (81.4)	174	50 (86.2)	180
Non-opioids				
Yes	69 (98.6)	258	57 (98.3)	218
No	14 (20.0)	14	7 (12.1)	9

[a] Patients with multiple analgesics used in the same category are counted only once in that category. Patients who used both types of analgesics are counted once in each of those categories.

[b] Per individual VOC event, if multiple analgesics in the same category are used, they are counted only once in that category. If both types of analgesics are used during one VOC event they are counted once in each of the 2 categories.

[c] Number of VOCs defined as the count of individual VOC events assessed throughout the treatment period from randomisation (Visit 2) to EOS visit or date of premature study discontinuation. VOC events with an onset date ≤ 7 days of the previous event onset date are counted as new events.

Analgesics: Percentage based on the total number of patients in the full analysis set with at least one individual VOC event, by treatment group.

Individual VOCs: Percentage based on the total number of patients in the full analysis set, by treatment group.

bd Twice daily; EOS, End of study; N, Total number of patients in treatment group; VOC Vaso-occlusive crisis.

Source: Table 14.2.1.2.7.

Source: Applicant submission

Patient Reported Outcomes/Quality of Life

Descriptive statistics for endpoints related to the PedsQL SCD Module (observed and change from baseline) are provided in Table 36.

Table 36 Analysis of PedsQL (Summary Statistics and Change from Baseline) (HESTIA3)

PedsQL SCD Module sub-scale/total score	Age group (years)[a]	Timepoint		Ticagrelor 15/30/45 mg bd (N=101) Observed	Ticagrelor 15/30/45 mg bd (N=101) Change from baseline	Placebo (N=92) Observed	Placebo (N=92) Change from baseline
Pain and hurt	>=2 to <5	Month 12	n	0	0	1	1
			Mean			100.00	25.00
			SD			NC	NC
			Median			100.00	25.00
			Min			100.0	25.0
			Max			100.0	25.0
	>=5 to <8	Baseline	n	24		14	
			Mean	79.17		80.56	
			SD	21.250		20.758	
			Median	80.56		88.89	
			Min	33.3		44.4	
			Max	100.0		100.0	
PedsQL SCD Module sub-scale/total score	Age group (years)[a]	Timepoint		Observed	Change from baseline	Observed	Change from baseline
Pain and hurt	>=5 to <8	Month 6	n	23	22	14	14
			Mean	86.47	10.35	89.29	8.73
			SD	16.139	22.893	14.366	18.035
			Median	94.44	2.78	100.00	5.56
			Min	50.0	-27.8	61.1	-22.2
			Max	100.0	66.7	100.0	44.4
		Month 12	n	2	2	1	1
			Mean	69.44	5.56	88.89	33.33
			SD	43.212	15.713	NC	NC
			Median	69.44	5.56	88.89	33.33
			Min	38.9	-5.6	88.9	33.3
			Max	100.0	16.7	88.9	33.3

[a] Age at randomisation (Visit 2).
Sub-scale scores computed as the sum of items' transformed scores divided by number of items included in each sub-scale and answered thereby accounting for missing data. If more than 50% of sub-scale items are missing [i.e. > (#items/2 – rounded down to the nearest integer)], sub-scale score is not computed.
PedsQL SCD Module total score (43/42/40 items - depending on version completed) is the mean of the transformed scores computed as the sum of the items' transformed scores divided by the number of items answered. If more than 50% of the items are missing (i.e. > 21/21/20 items for the SCD Module), the total score is not computed.
If the wrong version of the age-specific questionnaire is completed based on the patient's age at randomisation (Visit 2), the collected data is not included in the subsequent summary.
Baseline is the last assessment collected (scheduled or unscheduled) prior to the first dose of study treatment, or last assessment collected prior to or at the randomisation (Visit 2), for patients who are randomised but do not receive any treatment.
Visit based on planned protocol visit (number and name).
N Total number of patients in treatment group. n Number of patients included in analysis. Max Maximum. Min Minimum. SD Standard deviation. NC Not calculable. SCD Sickle cell disease. PedsQL Paediatric Quality of Life Inventory. bd Twice a day.

[Source: ASTRAZENECA\TICAGRELOR\LYA10053\BIOSTATISTICS\PRODUCTION\TABLES\EF214.SAS] (b) (4) 26NOV2020

Source: Applicant submission

The distribution of scores for PedsQL SCD was generally similar between treatment groups. The analysis of the secondary efficacy endpoints based on patient-reported outcomes did not demonstrate a pattern of difference between treatment groups in HRQL, fatigue or pain intensity during VOC. There was limited data available for many of the age categories and time points.

Dose/Dose Response

N/A

Durability of Response

N/A

Persistence of Effect

N/A

Additional Analyses Conducted on the Individual Trial

N/A

7 Integrated Review of Effectiveness

7.1 Assessment of Efficacy Across Trials

This section is not applicable because there was only one pivotal trial.

7.1.1 Primary Endpoints

N/A

7.1.2 Secondary and Other Endpoints

N/A

7.1.3 Subpopulations

N/A

7.1.4 Dose and Dose-Response

N/A

7.2 Additional Efficacy Considerations

7.2.1 Considerations on Benefit in the Postmarket Setting

This section is not applicable because the drug is not being marketed in the pediatric population.

7.2.2 Other Relevant Benefits

N/A

7.3 Integrated Assessment of Effectiveness

The primary endpoint for the Phase 3 study was not met. The proportion of patients reporting SAEs was higher on ticagrelor; this was driven by events of sickle cell anemia with crisis. In addition, 3 patients in the ticagrelor group and 1 patient in the placebo group died during the study. The study demonstrated no evidence of benefit for ticagrelor over placebo in the treatment of pediatric patients with SCD. The results of the primary efficacy analysis were consistent across the pre-defined subgroups. The study demonstrates an unfavorable benefit-risk profile for ticagrelor in children aged 2 years to <18 years with SCD.

8 Review of Safety

8.1 Safety Review Approach

HESTIA3 and HESTIA4 are both targeted toward a pediatric population. The clinical team has reviewed safety results of both studies. The applicant stated that HESTIA3 did not achieve the primary endpoint and is not seeking a pediatric indication. Therefore, the results of these trials were not verified down to the source data. Because ticagrelor was not effective in pediatric patients with sickle cell disease, detailed safety results will not be provided. The safety findings were reviewed to identify any unique safety signals in pediatric patients that would be important to include in labeling.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

Table 37 Safety Database for ticagrelor

Safety Database for Brilinta (ticagrelor) Individuals exposed to any treatment in this development program for the indication under review N=311		
Clinical Trial Groups	New Drug (n=211)	Placebo (n= 100)
Healthy Volunteers	44	0
Controlled Trials in Pediatric Patients with SCD	101	92
All other trials conducted for this indication	66	8
Controlled trials conducted for other indications	0	0

Source: Applicant submission

HESTIA 3

The duration of exposure to study treatment is summarized in Table 38. The duration of exposure was similar between the 2 treatment groups. Median total exposure was 296.5 days on ticagrelor and 288.0 days on placebo. Median actual exposure, which excludes missed exposure days due to treatment interruptions, was 289.5 days on ticagrelor and 283 days on placebo.

Table 38 Duration of Exposure (HESTIA3)

Overall dose level (15/30/45 mg bd)		**Ticagrelor 15/30/45 mg bd (N = 100)**	**Placebo (N = 92)**	**Total (N = 192)**
Total exposure (days)	n	100	92	192
	Mean	301.8	301.0	301.4
	SD	98.65	84.19	91.77
	Minimum	5	34	5
	1st quartile	265.5	267.0	267.0
	Median	296.5	288.0	296.0
	3rd quartile	335.0	332.0	334.0
	Maximum	598	548	598
Actual exposure (days)	n	100	92	192
	Mean	293.1	296.0	294.5
	SD	98.14	85.78	92.20
	Minimum	5	34	5
	1st quartile	263.5	261.0	262.0
	Median	289.5	283.0	287.5
	3rd quartile	334.0	328.0	331.5
	Maximum	598	547	598
Total exposure years		83.82	76.93	160.75

Total study treatment exposure (days) by overall dose level (includes missed exposure days due to study treatment interruptions): Exposure (days) = (date of last dose of study treatment minus date of first dose of study treatment) + 1.

Actual exposure (days) excludes missed exposure days due to study treatment interruptions.

Total exposure years (across patients per treatment group) = Sum (total study treatment exposure [days] by overall dose level) / 360.

bd, Twice daily; N, Total number of patients in treatment group; n, Number of patients included in analysis; SD, Standard deviation.

Source: derived from Table 14.3.1.1.

Source: Applicant submission

HESTIA4

Patients received a single oral dose of ticagrelor; 2 patients received 0.1 mg/kg and 19 patients received 0.2 mg/kg. All patients administered ticagrelor were included in the PK and safety

analysis.

8.2.2 Relevant characteristics of the safety population:

The development program has sufficient safety data in a broad population. Given the appropriately sized sample population among higher risk sickle cell disease patients, the safety data allows for generalizability of the safety findings. The demographic and other baseline disease characteristics are presented and discussed in further detail in Section 6.1.2 and Section 6.2. For HESTIA3, the demographic population was appropriately comparable between both treatment groups. The number of VOC's experienced by patients in each treatment group were similar. The number of patients that received both concomitant medications and disallowed concomitant medications were also equally distributed between the 2 treatment groups. However, the proportion of patients reporting disease-related medical history, notably blood and lymphatic systemic disorders, and infections was higher in ticagrelor vs placebo. Likewise, the proportion of patients reporting relevant surgical history, notably splenectomy, was higher in ticagrelor than in placebo.

8.2.3 Adequacy of the safety database:

The demography was as expected and similar to earlier studies in this population. Overall, the randomized treatment groups were balanced with respect to demographic characteristics at baseline. The size and adequacy of the safety database are acceptable. Dose exposure, duration of treatment, patient demographics and disease characteristics were all appropriate for each respective study.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

The OSI was not consulted to inspect clinical sites for this application because the applicant is not requesting an indication. There are no issues regarding data quality or the quality of the overall submission. However, it is worth emphasizing the applicant stated that HESTIA3 did not achieve the primary endpoint. Therefore, the results of this trial were not verified down to the source data. Data Quality and Integrity is further discussed in 6.2 "Data Quality and Integrity."

8.3.2 Categorization of Adverse Events

The applicant provided accurate definitions of AEs and serious adverse events (SAEs) in both study protocols.

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product, and which does not necessarily have a causal

relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in periods, even if no IMP has been administered.

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require
- medical intervention to prevent 1 of the outcomes listed above.

Serious Adverse events will be collected from the time of signature of informed consent throughout the treatment period and including the follow-up period. For HESTIA4, adverse events were collected starting from administration of IMP, and for HESTIA3, AEs were collected starting from the time of randomization.

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study center personnel: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the electronic case report form (eCRF). AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The definitions for intensity rating are:

- Mild (awareness of sign or symptom, but easily tolerated)

- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

Causality of 'related' was made if following a review of the relevant data, there was evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Reviewer Comment: These AE assessment strategies are appropriate.

For both HESTIA3 and HESTIA4 studies, verbatim terms were included in the data file and were translated well to the MedDRA preferred terms. HESTIA3 was translated to MedDRA version 23.0 and HESTIA4 was translated to MedDRA version 20.1.

Reviewer Comment: The applicant's coding does not seem to diminish safety signals through lumping or splitting of terms.

AE were organized by international order for system organ class (SOC) and preferred term.

For HESTIA3, adverse events were assessed by the number and percentage of patients with AEs, as well as by the event rate per 100 patient years (number of patients with AEs/ total exposure years) x 100 where exposure years for ticagrelor was 83.82 and placebo 76.93. Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in > 1 preferred term are counted once in each of those preferred terms.

For HESTIA4, adverse events were assessed by the number and percentage of patients with AEs. A patient can have one or more preferred terms reported under a given SOC. Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than 1 preferred term are counted once in each of those preferred terms.

Analyses of adverse events of interest for HESTIA3:
Severe hepatic impairment:
Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3×ULN together with total bilirubin ≥ 2×ULN need to be reported as SAEs, except if the elevation was caused by the underlying sickle cell disease, ie, hemolysis, as judged by the Investigator.

Bleeding Events:
Bleeding events were recorded as AEs. The Investigators classified bleeding events as major, clinically relevant non-major, or minor, as described below. Bleeding events were recorded in the eCRF.

For patients experiencing a bleeding event that fulfils criteria in more than 1 category, the bleed will be assigned to the most severe category. The bleeding definitions (Mitchell et al 2011) are:

- Major bleeding: defined as any fatal bleeding, clinically overt bleeding associated with a decrease in Hb of at least 20 g/L (2 g/dL), bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system or bleeding that requires surgical intervention in an operating suite.
- Clinically relevant non-major bleeding: defined as overt bleeding for which a blood product is administered, and which is not directly attributable to the patient's underlying medical condition, and bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite.
- Minor bleeding: defined as any overt or macroscopic evidence of bleeding that does not fulfil the above criteria for either major bleeding or clinically relevant, non-major bleeding. Menstrual bleeding resulting in a medical consultation and/or intervention will be classified as a minor bleeding event.

8.3.3 Routine Clinical Tests

An overview of the methodology and frequency of routine clinical testing is presented in Table 7 and Table 19.

Refer to section 8.3.2 for further discussion and detail on methodology of data collection of these studies.

Reviewer Comment: The safety assessment methods and time points described in each protocol appear reasonable and adequate.

8.4 Safety Results

8.4.1 Deaths

HESTIA3
Three patients in the ticagrelor group and 1 patient in the placebo group had an SAE with outcome of death. Key information on these 4 patients is provided in Table 39. One patient on ticagrelor was reported to have had a cerebrovascular accident with fatal outcome. The CT finding was interpreted as a subarachnoid bleed in the right hemisphere together with signs of meningitis. A second patient on ticagrelor was reported to have died suddenly (the Investigator reported this event as sudden death of unclear etiology). Since no imaging or autopsy was done, the exact cause of death is unclear. A third patient on ticagrelor was reported to have died from sepsis. The cause of death was confirmed by autopsy as meningitis and pneumonia. The Investigator concluded that the participant died of septicemia in the brain and lungs.

One patient on placebo was reported to have died of severe VOC after being hospitalized with severe general body pain and fever.

Table 39 Adverse Events with Outcome of Death (HESTIA3)

Patient identifier	Sex	Age (yrs) [a]	Event term as reported by the Investigator	AE (preferred term)	Time from first dose to AE (days)	Treatment period	Last dose level prior to death	Time from last dose to death (days)	Time from first dose to death (days)	Reasonable possibility AE caused by IP [b]
Treatment group: ticagrelor 15/30/45 mg bd										
(b) (6)	Female	17	Cerebral vascular accident	Cerebrovascular accident	296	On-treatment	30 mg bd	6	300	No
	Male	7	Septicaemia	Sepsis	264	On-treatment	15 mg bd	2	265	No
	Male	10	Sudden death of unclear aetiology	Sudden death	309	On-treatment	30 mg bd	1	309	Yes
Treatment group: placebo										
(b) (6)	Female	15	Sickle cell anaemia with crisis	Sickle cell anaemia with crisis	130	On-treatment	30 mg bd	2	131	No

[a] Age at randomisation (Visit 2).
[b] Causality as assessed by the Investigator.
Pre-treatment: AEs with onset date < date of first dose of study treatment.
On-treatment: AEs with onset date ≥ the date of first dose of study treatment and ≤ the date of last dose of study treatment + 7 days.
Off-treatment: AEs occurring off-treatment ie, onset date > the date of last dose of study treatment + 7 days.
Includes all adverse events with outcome of death that occurred during the study.
MedDRA version 23.0.
AE, Adverse event; bd, twice daily; IP, Investigational product.
Source: Table 14.3.3.2.

Source: Applicant submission

HESTIA4
There were no deaths in this study.

8.4.2 Serious Adverse Events

HESTIA3
The number and percentage of patients with SAEs on-treatment is summarized by SOC and preferred term in Table 40. The SOCs most commonly reported for SAEs were: Blood and lymphatic system disorders (39 patients (39.0%) in the ticagrelor group versus 28 (30.4%) in the placebo group) and Infections and infestations (18 patients (18.0%) in the ticagrelor group versus 8 (8.7%) in the placebo group).

The most commonly reported SAE was sickle cell anemia with crisis: 39 patients (39.0%) in the ticagrelor group versus 24 (26.1%) in the placebo group. In summary, there was a higher proportion of reported SAEs for patients in the ticagrelor group compared with placebo. This was driven by the reports of sickle cell anemia with crisis.

Table 40 Patient with Serious Adverse Events (HESTIA3)

System organ class/ preferred term	Number (%) of patients [a]	
	Ticagrelor 15/30/45 mg bd (N = 100)	Placebo (N = 92)
Patients with any SAE	44 (44.0)	29 (31.5)
Infections and infestations	18 (18.0)	8 (8.7)
Atypical pneumonia	1 (1.0)	0
Bronchitis	1 (1.0)	1 (1.1)
Cellulitis	3 (3.0)	0
Gastroenteritis	0	1 (1.1)
Influenza	0	2 (2.2)
Malaria	4 (4.0)	1 (1.1)
Meningitis	1 (1.0)	0
Nasopharyngitis	1 (1.0)	0
Pharyngotonsillitis	1 (1.0)	0
Pneumonia	4 (4.0)	0
Respiratory syncytial virus infection	0	1 (1.1)
Respiratory tract infection viral	1 (1.0)	0
Sepsis	6 (6.0)	1 (1.1)
Upper respiratory tract infection	1 (1.0)	0
Urinary tract infection	0	1 (1.1)
Viral infection	1 (1.0)	0
Blood and lymphatic system disorders	39 (39.0)	28 (30.4)

System organ class/ preferred term	Number (%) of patients [a]	
	Ticagrelor 15/30/45 mg bd (N = 100)	Placebo (N = 92)
Anaemia	6 (6.0)	7 (7.6)
Hypersplenism	0	3 (3.3)
Pancytopenia	0	1 (1.1)
Sickle cell anaemia with crisis	39 (39.0)	24 (26.1)
Nervous system disorders	1 (1.0)	0
Cerebrovascular accident	1 (1.0)	0
Respiratory, thoracic and mediastinal disorders	2 (2.0)	0
Atelectasis	1 (1.0)	0
Bronchospasm	1 (1.0)	0
Gastrointestinal disorders	2 (2.0)	1 (1.1)
Abdominal distension	0	1 (1.1)
Constipation	2 (2.0)	0
Skin and subcutaneous tissue disorders	1 (1.0)	0
Pemphigoid	1 (1.0)	0
Musculoskeletal and connective tissue disorders	2 (2.0)	1 (1.1)
Osteonecrosis	2 (2.0)	1 (1.1)
General disorders and administration site conditions	3 (3.0)	3 (3.3)
Pyrexia	2 (2.0)	3 (3.3)
Sudden death	1 (1.0)	0
Investigations	0	1 (1.1)
Haemoglobin decreased	0	1 (1.1)
Injury, poisoning and procedural complications	1 (1.0)	0
Jaw fracture	1 (1.0)	0
Post-traumatic pain	1 (1.0)	0
Road traffic accident	1 (1.0)	0

[a] Number (%) of patients with SAEs, sorted by international order for system organ class and alphabetical order for preferred term within system organ class.

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in > 1 preferred term are counted once in each of those preferred terms.

Adverse events on-treatment: AEs with onset date ≥ date of first dose of study treatment and ≤ date of last dose of study treatment + 7 days.

Percentage based on total number of patients in the safety analysis set, by treatment group.

MedDRA version 23.0.

AE, adverse event; bd, Twice daily; N, Total number of patients in treatment group; SAE, serious adverse event.

Source: Table 14.3.4.2.1.

Source: Applicant submission

HESTIA4
One patient had an SAE.

Patient [redacted], a 16-month-old white female experienced an AE of bronchiolitis on study Day 6. The bronchiolitis was considered by the Investigator to be of moderate intensity and not related to treatment; the duration of the event was 6 days. The patient was hospitalized on study Day 8, the day of the follow-up visit ([redacted]), due to fever and productive cough caused by viral infection. The bronchiolitis fulfilled the SAE criteria due to the hospitalization of the patient 7 days after administration of a single oral dose of 0.2 mg/kg ticagrelor on [redacted] The patient had SCD genotype HbSS diagnosed [redacted] and had no relevant surgical history or ongoing medical history. Medication on entry and during the study included: hydroxycarbamide, folic acid, amoxicillin, cefixime and paracetamol.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

HESTIA3
Key information relating to the patients who had discontinuation of study drug due to AEs (DAEs) is provided in Table 41. DAEs were few (4 in each treatment group).

Table 41 Adverse Events Leading to Discontinuation of IP (HESTIA3)

Patient identifier	Sex	Age (yrs) [a]	Event term as reported by the Investigator	AE (preferred term)	Last dose level prior to onset of on-treatment AE	Time from first dose to onset of AE (days)	Time from first dose to discontinuation of IP (days)	SAE	Outcome	Reasonable possibility AE caused by IP [b]
Treatment group: ticagrelor 15/30/45 mg bd [c]										
(b) (6)	Male	8	Sickle cell anaemia with crisis	Sickle cell anaemia with crisis	15 mg bd	96	101	Yes	Recovered/Resolved	No
	Female	17	Cerebral vascular accident	Cerebrovascular accident	30 mg bd	296	295	Yes	Fatal	No
	Male	7	Septicaemia	Sepsis	15 mg bd	264	264	Yes	Fatal	No
	Male	10	Sudden death of unclear aetiology	Sudden death	30 mg bd	309	309	Yes	Fatal	Yes
Treatment group: placebo										
(b) (6)	Female	12	Bell's palsy	Facial paralysis	30 mg bd	357	363	No	Recovered/Resolved	No
	Female	17	Raised bilirubin	Blood bilirubin increased	30 mg bd	17	34	No	Recovered/Resolved	No
	Male	12	Avascular osteonecrosis of radial bone	Osteonecrosis	30 mg bd	315	330	Yes	Not Recovered/Not Resolved	No
	Female	15	Sickle cell anaemia with crisis	Sickle cell anaemia with crisis	30 mg bd	130	130	Yes	Fatal	No

[a] Age (years) at randomisation (Visit 2).
[b] Causality as assessed by the Investigator.
[c] Patients initially treated according to their weight at randomisation (Visit 2), during the study if the patient's weight changes, their dose level changes accordingly. Patients presented by actual treatment group.
AE, Adverse event; bd, Twice daily; IP, Investigational product; SAE, Serious AE.
MedDRA version 23.0.
Source: Table 14.3.5.2.

Source: Applicant submission

HESTIA4
Patients received a single dose of study drug. None of the patients were discontinued due to an AE.

8.4.4 Significant Adverse Events

In HESTIA3 and HESTIA4, there were no adverse events of significant interest.

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

HESTIA3
The number of patients with adverse events (AEs) in any category is summarized overall in Table 42. The proportion of patients with AEs was similar between the 2 treatment groups and also similar between the 2 treatment groups both within and across the 2 age groups. A higher proportion of patients reported SAEs in the ticagrelor group: 44 patients (44%) on ticagrelor versus 29 (31.5%) on placebo.

Table 42 Number of Patients with Adverse Events

Adverse event category	Number (%) of patients [a]	
	Ticagrelor 15/30/45 mg bd (N = 100)	Placebo (N = 92)
Any AE	95 (95.0)	84 (91.3)
AE causally related to IP	6 (6.0)	2 (2.2)
AE with maximum intensity [b]	95 (95.0)	84 (91.3)
Mild	21 (21.0)	16 (17.4)
Moderate	32 (32.0)	39 (42.4)
Severe	42 (42.0)	29 (31.5)
Any AE with outcome = death	3 (3.0)	1 (1.1)
Any SAE (including events with outcome = death)	44 (44.0)	29 (31.5)
Any AE leading to discontinuation of IP	4 (4.0)	4 (4.3)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in > 1 category are counted once in each of those categories.

[b] Patients with multiple events in the same category are counted only once in the maximum intensity category. Patients with events in > 1 category are counted once in each of those categories.

Adverse events on-treatment: AEs with onset date ≥ date of first dose of study treatment and ≤ date of last dose of study treatment + 7 days.

Percentage based on total number of patients in the safety analysis set, by age group and treatment group.

AE, Adverse event; bd, Twice daily; IP, Investigational Product; N, Total number of patients in treatment group; SAE, Serious adverse event.

Source: derived from Table 14.3.2.1.1.

Source: Applicant submission

The most commonly reported AEs (with frequency ≥ 10% of patients in either treatment group) are summarized by SOC and PT in Table 43. The most commonly reported SOCs were Blood and lymphatic system disorders: 74 patients (74.0%) on ticagrelor, and 64 (69.6%) on placebo, and Infections and Infestations: 53 patients (53.0%) on ticagrelor and 52 (56.5%) on placebo.

For the SOC Blood and lymphatic system disorders, the most common preferred term was sickle cell anemia with crisis: 71 patients (71.0%) on ticagrelor, and 57 patients (62.0%) on placebo. This AE of sickle cell anemia with crisis reflect the underlying disease in this patient population. The most common preferred terms reported in the Infections and infestations SOC were Upper respiratory tract infection: 20 patients (20.0%) on ticagrelor versus 24 (26.1%) on placebo, and Malaria: 15 patients (15.0%) on ticagrelor versus 8 (8.7%) on placebo.

The proportion of patients reporting AEs in the following SOCs was higher for ticagrelor than for placebo:

- Blood and lymphatic system disorders: 74 patients (74.0%) on ticagrelor versus 64 (69.6%) on placebo
- Musculoskeletal and connective tissue disorders: 47 patients (47.0%) on ticagrelor versus 37 (40.2%) on placebo
- Respiratory, thoracic and mediastinal disorders: 31 patients (31.0%) on ticagrelor versus 16 (17.4%) on placebo
- Gastrointestinal disorders: 30 patients (30.0%) on ticagrelor versus 24 (26.1%) on placebo.

The most commonly reported preferred term in the SOC of Musculoskeletal and connective tissue disorders were Pain in extremity (28 patients [28.0%] on ticagrelor vs 23 [25.0%] on placebo) and Back pain (21 patients [21.0%] on ticagrelor vs 12 [13.0%] on placebo).

The most commonly reported preferred term in the SOC of Respiratory, thoracic and mediastinal disorders was Cough (17 patients [17.0%] on ticagrelor versus 7 [7.6%] on placebo).

The most commonly reported preferred term under Gastrointestinal disorders was Abdominal pain (15 patients [15.0%] on ticagrelor versus 10 [10.9%] on placebo).

Table 43 Most Commonly Reported AE (Frequency ≥ 10%) (HESTIA3)

System organ class / preferred term	Ticagrelor 15/30/45 mg bd (N = 100)		Placebo (N = 92)	
	Number (%) of patients [a]	Event rate (per 100 patient years) [b]	Number (%) of patients [a]	Event rate (per 100 patient years) [b]
Patients with any AE	95 (95.0)	113.34	84 (91.3)	109.20
Infections and infestations	53 (53.0)	63.23	52 (56.5)	67.60
Malaria	15 (15.0)	17.90	8 (8.7)	10.40
Upper respiratory tract infection	20 (20.0)	23.86	24 (26.1)	31.20
Blood and lymphatic system disorders	74 (74.0)	88.28	64 (69.6)	83.20
Anaemia	10 (10.0)	11.93	11 (12.0)	14.30
Sickle cell anaemia with crisis	71 (71.0)	84.70	57 (62.0)	74.10
Nervous system disorders	24 (24.0)	28.63	23 (25.0)	29.90
Headache	24 (24.0)	28.63	18 (19.6)	23.40
Respiratory, thoracic and mediastinal disorders	31 (31.0)	36.98	16 (17.4)	20.80
Cough	17 (17.0)	20.28	7 (7.6)	9.10
Gastrointestinal disorders	30 (30.0)	35.79	24 (26.1)	31.20
Abdominal pain	15 (15.0)	17.90	10 (10.9)	13.00
Musculoskeletal and connective tissue disorders	47 (47.0)	56.07	37 (40.2)	48.10
Arthralgia	14 (14.0)	16.70	14 (15.2)	18.20
Back pain	21 (21.0)	25.05	12 (13.0)	15.60
Pain in extremity	28 (28.0)	33.40	23 (25.0)	29.90
General disorders and administration site conditions	27 (27.0)	32.21	24 (26.1)	31.20
Pyrexia	13 (13.0)	15.51	13 (14.1)	16.90

[a] Number (%) of patients with AEs, sorted by international order for system organ class and alphabetical order for preferred term within system organ class.

[b] Event rate per 100 patient years = (number of patients with AEs/total exposure years) × 100 where exposure years: ticagrelor = 83.82 and placebo = 76.93.

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in > 1 preferred term are counted once in each of those preferred terms.

Adverse events on-treatment: AEs with onset date ≥ date of first dose of study treatment and ≤ date of last dose of study treatment + 7 days.

Percentage based on total number of patients in the safety analysis set, by treatment group.

MedDRA version 23.0.

AE, Adverse event; bd, Twice daily; N, Total number of patients in treatment group.

Source: derived from Table 14.3.2.2.1.

Source: Applicant submission

HESTIA4
The 2 patients aged <6 months administered 0.1 mg/kg ticagrelor did not experience AEs.

Twelve AEs were experienced by 6 (31.6%) patients administered 0.2 mg/kg ticagrelor (3 AEs by 3 (50%) patients aged 6 months to <12 months and 9 AEs by 3 (23.1%) patients aged 12 months to <24 months). One (5.3%) patient (16-months-old white female) experienced an SAE of bronchiolitis 7 days after administration of ticagrelor (Section 12.3.2). Pallor and viral upper respiratory tract infection were each reported by 2 (10.5%) patients; the other AEs were each experienced by 1 (5.3%) patient on single occasions. None of the events was considered by the Investigator related to treatment or of severe intensity. Moderate AEs were experienced by 3 (50%) patients aged 6 months to <12 months and 2 (15.4%) patients aged 12 months to <24 months.

Adverse events experienced by patients in each of the categories are summarized in Table 44.

Table 44 Number of Patients with Adverse Events (HESTIA4)

	Number (%) of patients[a]				
	Ticagrelor single oral 0.1 mg/kg dose	Ticagrelor single oral 0.2 mg/kg dose			Total
	<6 months old	6 to <12 months old	12 to <24 months old	Total	
AE category	(N=2)	(N=6)	(N=13)	(N=19)	(N=21)
Any AE	0	3 (50.0)	3 (23.1)	6 (31.6)	6 (28.6)
Any AE with outcome=death	0	0	0	0	0
Any SAE (including events with outcome=death)	0	0	1 (7.7)	1 (5.3)	1 (4.8)
Any AE causally related to IP	0	0	0	0	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
Percentages are calculated out of total number of patients in each treatment and age combination group.
This includes only on-treatment AEs (i.e., onset date ≥date of single oral ticagrelor dose and up to and including 7 days following last dose).
AE: adverse event; IP: investigational product; N: number of patients in treatment and age combination group; SAE: serious AE.
Source: Table 11.3.2.1.

Source: Applicant submission

The number of patients with AEs by system organ class and preferred term is summarized in Table 45. None of the events was considered by the Investigator to be related to treatment or of severe intensity.

Moderate AEs were experienced by 3 (50%) patients aged 6 months to <12 months and 2 (15.4%) patients aged 12 months to <24 months:
• Bronchiolitis 1 (7.7%) patient aged 12 months to <24 months.
• Pallor 1 (16.7%) patient aged 6 months to <12 months and 1 (7.7%) patient aged 12 months to <24 months.
• Viral upper respiratory tract infection 2 (33.3%) patients aged 6 months to <12 months.

Table 45 Number of Patients with AE by System Organ Class and Preferred Term (HESTIA4)

[a] Number (%) of patients are sorted by international order for SOC and alphabetically for PT. A patient can have one or more PTs reported under a given SOC.
[b] Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than 1 PT are counted once in each of those PT.
Percentages are calculated out of total number of patients in each treatment and age combination group.
This includes only on-treatment AEs (ie, onset date ≥date of single oral ticagrelor dose and up to and including 7 days following last dose).
MedDRA version 20.1.
AE: adverse event; N: number of patients in treatment and age combination group; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class.
Source: Table 11.3.2.2.

Source: Applicant submission

8.4.6 Laboratory Findings

HESTIA3
Clinical laboratory results are presented separately for hematology, clinical chemistry, and urinalysis variables.

In some cases, due to local regulations and the COVID-19 pandemic it was necessary to use local/regional laboratories for analysis, which resulted in values displayed in different units and accordingly presented in separate tables. In the different sub-headings, the conclusions were derived taking all laboratory data available into consideration. Laboratory data are presented in summary tables independent of age category.

Hematology
Changes in Hematology Values over Time
Overall, there were no clinically important changes in mean or median values of any hematology variable over time, in patients on ticagrelor compared to placebo. Baseline hematocrit and hemoglobin values were generally low compared with the reference range for healthy subjects. This is expected in patients with SCD.

Changes in Hematology Values in Individual Patients over Time
There were no trends or individual abnormalities associated with administration of ticagrelor for any hematology parameters. Small numbers of patients in each treatment group changed from normal to high or low values (defined according to laboratory reference ranges) during the study with the majority presenting with no shift in category. There were no clinically relevant differences between the treatment groups in the pattern and frequency of patients shifting from normal to high or low values.

Individual Clinically Important Abnormalities
Except for the low hematocrit and hemoglobin values in some patients at baseline, there were no individual clinically important abnormalities in hematology values in any patient.

Clinical Chemistry
Changes in Clinical Chemistry Values over Time
Overall, there were no clinically important changes in mean or median values of any clinical chemistry parameter over time. Of note is that one patient in the placebo-group had a single lactate dehydrogenase value of 388 ukat/L, affecting the mean value, although there was no clinically significant change in the median value over time.

Changes in Clinical Chemistry Values in Individual Patients Over Time
There were no trends or individual abnormalities associated with administration of ticagrelor for any clinical chemistry parameter. Small numbers of patients in each treatment group changed from normal to high or low values (defined according to laboratory reference ranges) during the study. There were no clinically relevant differences between the treatment groups in the pattern and frequency of patients shifting from normal to high or low values.

Individual Clinically Important Abnormalities in Clinical Chemistry
There were no individual clinically important abnormalities in clinical chemistry values in any patient, except for the one patient on placebo with an increase in lactate dehydrogenase.

Elevations in Alanine Aminotransferase or Aspartate Aminotransferase Accompanied by Elevations in Total Bilirubin
The number and percentage of patients experiencing increases in liver enzymes ALT, AST, and bilirubin based on multiples of the ULN is summarized below.

Forty-two patients in the ticagrelor group, compared to 51 patients in the placebo group, had an increase of bilirubin ≥ 2 ULN, as could be expected in a population of patients with SCD.

Table 46 Number of Patients with Elevated Liver Test Results On-Treatment

Category	Number (%) of Patients	
	Ticagrelor 15/30/45 mg bd (N = 100)	Placebo (N = 92)
Patients with on-treatment ALT, AST or total bilirubin observed values	100 (100)	92 (100)
Patients with at least one elevated liver function test result on-treatment	42 (42.0)	51 (55.4)
AST elevation	98	92
< 3 × ULN	98 (100.0)	92 (100.0)
≥ 3 × ULN to < 5 × ULN	0	0
≥ 5 × ULN to < 10 × ULN	0	0
≥ 10 × ULN	0	0
ALT elevation	98	92
< 3 × ULN	98 (100.0)	92 (100.0)
≥ 3 × ULN to < 5 × ULN	2 (2.0)	0
≥ 5× ULN to < 10 × ULN	0	0
≥ 10 × ULN	0	0
AST or ALT elevation	98	92
< 3 × ULN	98 (100.0)	92 (100.0)
≥ 3 × ULN to < 5 × ULN	2 (2.0)	0
≥ 5× ULN to < 10 × ULN	0	0
≥ 10 × ULN	0	0
Total Bilirubin elevation	98	92
≥ 2 × ULN	42 (42.9)	51 (55.4)
AST/ALT or Total Bilirubin elevation	98	92
(ALT ≥ 3× ULN or AST ≥ 3× ULN) and (TBL ≥ 2× ULN)	2 (2.0)	0

Percentage based on the total number of patients in the safety analysis set with at least one post-baseline on-treatment value, by treatment group and liver function test.
Elevated ALT, AST and total bilirubin: Based on liver function test results (scheduled or unscheduled) observed within the period from the first dose of study treatment up to and including the last dose of study treatment + 7 days.
ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; bd, Twice daily; N, Total number of patients in treatment group; TBL, Total bilirubin; ULN, Upper limit of normal.
Source Table 14.3.7.4.2.

Source: Applicant submission

Two patients in the ticagrelor group had elevations of liver function tests on-treatment meeting criteria for potential Hy's law. However, both had alternative explanations for the abnormal values, thus did not meet the full criteria for Hy's Law.

Patient (b) (6): Combined marked elevations in ALT and TBL were observed. At the Week 4 Visit, (Study Day 29), the patient had an ALT value of 2.50 ukat/L (3.49 × ULN), AST of 1.57 ukat/L (2.35 × ULN) and a TBL value of 51.0 umol/L (2.4 × ULN). Treatment with ticagrelor was continued. At the Month 6 visit (Day 176) the values had decreased, ALT value of 0.42 ukat/L (0.58 × ULN), AST of 0.67 ukat/L (1.0 × ULN) and a TBL value of 34.0 umol/L (1.6 × ULN) and also at the safety follow-up visit (Day 379). The elevated liver function tests occurred in connection with an event of sickle cell anemia with crisis which is a likely explanation of the laboratory finding.

Patient (b) (6): The patient had combined marked elevations in ALT and TBL at the Month 6 visit (Study Day 184); ALT value of 2.30 ukat/L (3.37 × ULN), AST of 1.78 ukat/L (2.68 × ULN) and a TBL value of 66.9 umol/L (3.3 × ULN). At the safety follow-up visit (Day 331) the ALT value had decreased, 0.83 ukat/L (1.25 × ULN) and the TBL value remained elevated, 63.3 ukat/L (3.1 × ULN). The patient was diagnosed with Hepatitis C in connection with the elevated liver function tests, which is a likely explanation for the laboratory finding. There was no interruption to treatment and ticagrelor was continued.

Urinalysis
There were no clinically important abnormalities observed in the urinalysis.

HESTIA4
Clinical laboratory evaluations were performed at baseline (pre-dose) and follow-up. Hematocrit and hemoglobin values were generally low compared with the reference range for healthy subjects. This is expected in patients with SCD. There were no clinically relevant changes from baseline to follow-up for the hematology or serum chemistry evaluations including evaluation of the liver chemistry. There were no increases of ALT/AST and bilirubin fulfilling Hy's law criteria. Coagulation was performed at baseline (pre-dose) to confirm eligibility of the patients (exclusion criterion 6: INR >1.4) INR values ranged from 0.010 to 1.363.

8.4.7 Vital Signs

HESTIA3
No clinically relevant changes from baseline were observed for systolic and diastolic BP or pulse in either treatment group.

HESTIA4
Vital signs (systolic and diastolic BP, pulse, body temperature and body weight) were measured at screening, baseline (pre-dose) and follow-up. None of the changes in vital signs measurements were considered by the Investigator to be treatment related.

8.4.8 Electrocardiograms (ECGs)

HESTIA3
There were no trends or individual abnormalities for any ECG parameter, except for one abnormal ECG in patient (b) (6) in the ticagrelor group. At the Month 6 visit (study Day 183), the ECG was considered abnormal with right ventricular hypertrophy and left ventricular hypertrophy. At the safety follow-up visit the ECG was interpreted as abnormal, showing pulmonary hypertension. Study treatment was not interrupted.

HESTIA4

The ECG results were normal at screening in 19 patients, and abnormal, but not clinically significant in 2 (9.5%) patients. None of the ECG abnormalities were reported as AEs. There were no clinically significant ECG results. There were no ECG's obtained post-dose.

8.4.9 QT

N/A for efficacy supplement.

8.4.10 Immunogenicity

N/A

8.5 Analysis of Submission-Specific Safety Issues

Detailed safety results not provided due to efficacy not being demonstrated and no indication granted.

8.6 Safety Analyses by Demographic Subgroups

8.6.1 Pediatrics and Assessment of Effects on Growth

Pediatric Exclusivity was granted for studies conducted on ticagrelor as of April 8, 2022. The sponsor was notified via letter.

8.6.2 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

An overdose of ticagrelor may lead to any of the AE's described in section 8.4.2 or 8.4.4. There were no overdose cases in either the HESTIA3 or HESTIA4 study. Ticagrelor has not neurologic effects and thus is not likely to be abused.

8.7 Safety in the Postmarket Setting

8.7.1 Safety Concerns Identified Through Postmarket Experience

N/A; not being marketed in pediatric patients.

8.7.2 Expectations on Safety in the Postmarket Setting

N/A; not being marketed in pediatric patients.

8.7.3 Additional Safety Issues From Other Disciplines

N/A

8.8 Integrated Assessment of Safety

N/A

9 Advisory Committee Meeting and Other External Consultation

No advisory committee was convened because the applicant was not seeking an indication.

10 Labeling Recommendations

10.1 Prescription Drug Labeling

The USPI was updated with a description of the failed pediatric trial in Section 8.4. Labeling negotiations have not been finalized as of the date of this review.

10.2 Nonprescription Drug Labeling

N/A

11 Postmarketing Requirements and Commitments

This is not applicable because we are not approving a new indication.

12 Risk Evaluation and Mitigation Strategies (REMS)

This is not applicable because we are not approving a new indication.

13 Appendices

13.1 References

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13.2 Financial Disclosure

Table 47 Financial Disclosure HESTIA3/ D5136C00009

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 277		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 19		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason?	Yes ☒	No ☐ (Request explanation from Applicant)

Table 48 Financial Disclosure HESTIA4/ D5136C00010

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 61		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 17		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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